Preparative Routes to C-Homosteroids

by

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A Thesis presented for the Degree of Doctor of Philosophy

University of Edinburgh September, 1976

Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

This thesis describes results of research carried out in the Department of Chemistry, University of Edinburgh under the supervision of Dr. P.J. Sykes between October 1971 and September 1974.

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The following courses were attended during the three years of research:

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Dr. A.J. Bellamy (5 lectures)

Organometallic Reagents in Organic Synthesis,

Prof. P.L. Pauson (5 lectures)

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Dr. B. Capon (5 lectures)

Colloids and Money,

Dr. A. Pethica and Dr. P. Anderson (5 lectures)

Industrial Research and Development

Dr. B. Gravenor (5 lectures)

^{13}C and Fourier Transform n.m.r. Spectroscopy,

Dr. D.G. Shaw (5 lectures)

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Summary

The principal object of the work described in this thesis has been the investigation of synthetic routes leading to C-homosteroids.

Until now only two routes were known for the preparation of homocyclic C-homosteroids one of which was a photochemical rearrangement and the other a complicated series of reactions including opening and reclosing of the C-ring. The Tiffeneau-Demjanov reaction, used to make the first homosteroids and which involved the rearrangement of the 3-aminomethyl-3-hydroxy derivatives of thecorresponding 3-ketones, were found to form mixtures of the 3- and 4-keto ring-A expanded compounds. Repitition of this work with cholestan-3-one as starting material in fact showed the two components of the final product mixture, namely A-homocholestan-3-one and A-homocholestan-4-one to be distinguishable by n.m.r. which confirmed previous O.R.D. and circular dichroism results which had suggested the presence of these two ketones in an approximately 50:50 mixture.

Application of this scheme to hecogenin acetate, a 12-keto sapogenin required the formation of the 12-aminomethyl-12-hydroxy derivative which was prepared by two separate routes. The subsequent rearrangement led to C-homohecogenin and its acetate the spectra of which suggested the preferential if not exclusive formation of the 12-keto-C-homosteroid opposed to the 12a-ketone.

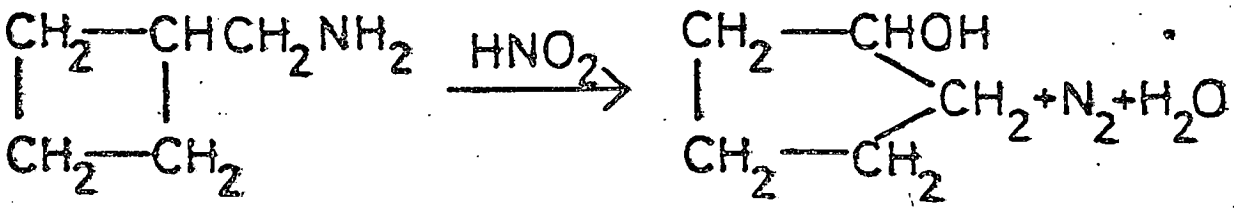
Carbene additions to the enol acetates and ethers followed by rearrangement was also known as a method for steroid A, B and D-ring enlargement. Rearrangement of the product of dichlorocarbene addition to 3β, 12,20β-triacetoxy-pregn-11-ene furnished 3β,20β-dihydroxy-C-homopregn-12a-one in the same way. The carbene addition however was dependent on

substituents in ring-D and on the position of the double-bond in ring-C to which the carbene was to add, the $\Delta^{11,12}$ enol acetate adding carbene whereas the $\Delta^{9,11}$ enol acetate did not.

Finally, exocyclic epoxides and tosyl hydrazones of ring-D were found to react under various conditions suitable forWagner-Meerwein rearrangement with the subsequent formation of C-homo-18-nor derivatives in varying yields.

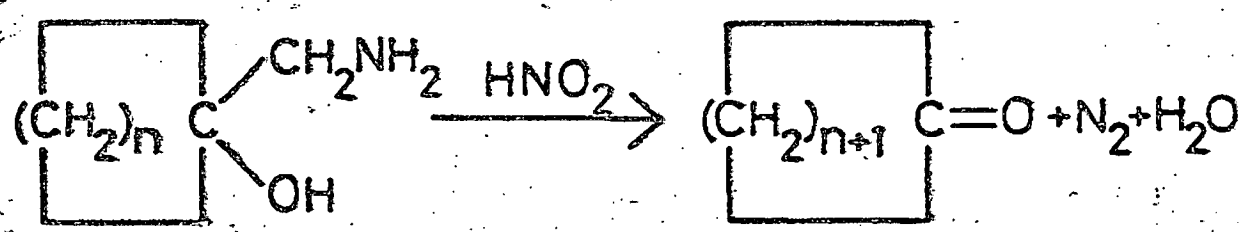
1. Introduction

The reaction of aminomethylcycloalkanes with nitrous acid to produce cycloalkanols in which the ring is larger by one carbon atom is known as the Demjanov rearrangement Scheme 1 first discovered in 1901 by Demjanov and Luschnikov[1], but not recognised until 1903[2] when cyclopentanol was identified as one of the products formed from reaction of nitrous acid with cyclobutane methylamine.



Scheme 1

An extension of this reaction, reported by Tiffeneau, Weill and Tchoubar[3] in 1937, consists of the nitrous acid deamination of 1-aminomethylcycloalkanols to form the ring-enlarged ketones. Scheme 2.

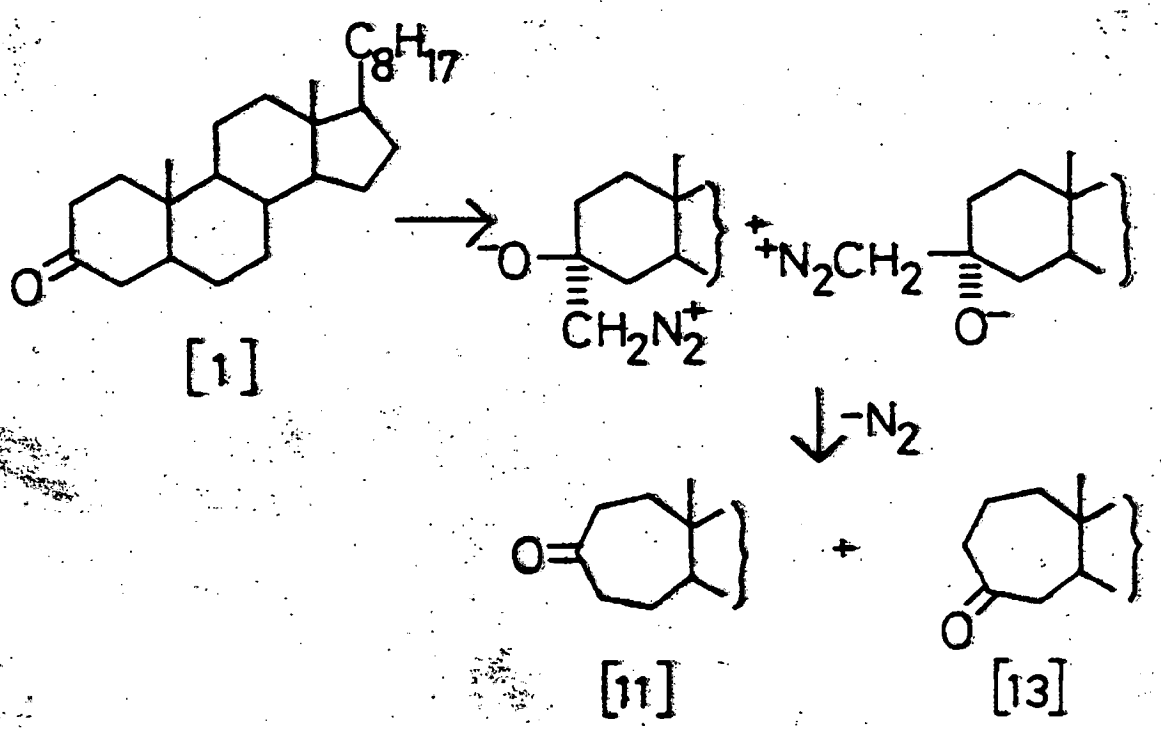


Scheme 2

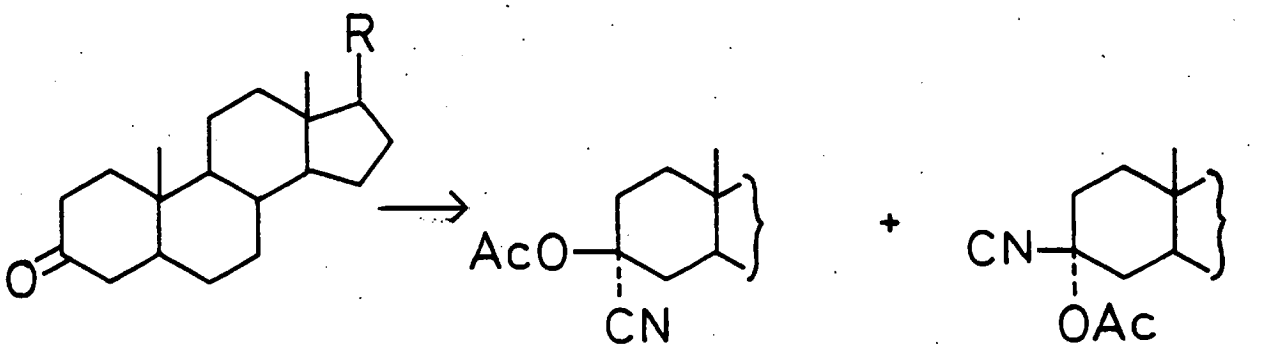
This became known as the Tiffeneau-Demjanov reaction and was employed by Goldberg and Kirchensteiner[4] in 1943 to prepare the first A-homo steroids. The position of the ketone in the A-homocholestanone and A-homo-17-acetoxyandrostanone produced was unable to be assigned to carbon three or carbon four. The 3-aminomethyl-3-alcohols required for

rearrangement to the products were prepared from the mixture of cyanohydrins, 3α-cyano-cholestan-3β-ol and 3β-cyano-cholestan-3α-ol prepared from cholestan-3-one by treatment with potassium cyanide and acetic acid. The epimeric mixtures were hydrogenated in the presence of a catalyst to give 3α-aminomethyl-cholestan-3β-ol (7) and its 3β-aminomethyl-3α-alcohol epimer (9) and 3α-aminomethyl-androstan-3β-ol (8) and the 3β aminomethyl-3α-alcohol (10).

Nelson and Schut[5] reported these reactions using the acetylated cyanohydrins of cholestan-3-one (3) and (5). When this type of reaction is applied to an unsymmetrical ketone, it is generally possible to isolate two homologated ketones from the reaction since the introduction of the extra methylene group may take place at either of the two sites adjacent to the parent carbonyl group and in many instances it was found that exocyclic epoxide by-products were formed. These features



Scheme 3

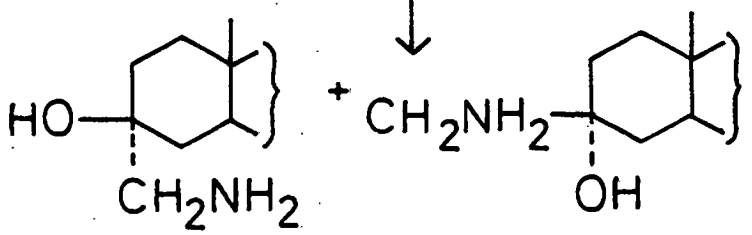


R=C_8H_{17} [1]
R=OH [2]

R=C_8H_{17} [3]
R=OAc [4]

R=C_8H_{17} [5]
R=OAc [6]

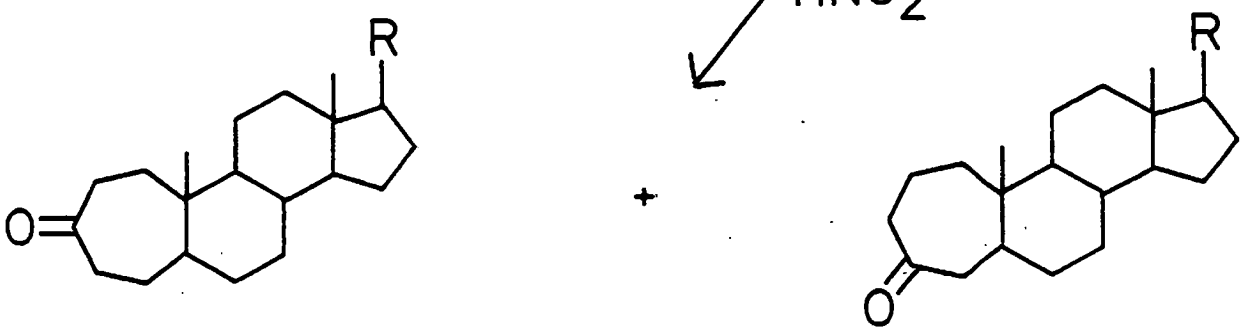
$LiAlH_4$



R=C_8H_{17} [7]
R=OH [8]

R=C_8H_{17} [9]
R=OH [10]

HNO_2



R=C_8H_{17} [11]
R=OH [12]

R=C_8H_{17} [13]
R=OH [14]
R=OAc [28]

Scheme 4

were also found common to the ring-expansion reactions of cyclic ketones with diazo compounds. However, Nelson and Schut found A-homocholestan-4-one as the major product but no A-homocholestan-3-one the other expected homologated ketone. However, they were able to find both ring-A expanded ketones using the one stage diazomethane reaction. Scheme 3 . The A-homocholestan-3-one arises from C-4 migration and A-homocholestan-4-one from C-2 migration. The assignment of position to the carbonyls was done by a study of the fingerprint region in the infra-red spectra.

Jones and Price[6], in 1969, following the need to prepare A-homosteroids for study to evaluate the electronic and structural specificities of the enzymes of steroid metabolism, prepared the ring-A expanded androstane ketones as had Goldberg and Kirchensteiner by the Tiffeneau-Demjanov reaction and were able to isolate both A-homo-androstan-3-one (12) and A-homoandrostan-4-one (14) from the product mixture.

Sykes *et al.*[9], in 1970, repeating the Tiffeneau-Demjanov ring expansion of 3-aminomethyl-5α-cholestan-3-ol, found the same apparently contradictory results to those expected as had Nelson and Schut, in that only one homologated ketone, A-homo-5α-cholestan-4-one, was produced. The series of reactions were carried out by the same methods as previous workers[4,5,6] starting from cholestan-3-one, except that the cyanohydrins were made by exchange with acetone cyanohydrin,[10] the isomers being acetylated and separated, the following hydrogenation and rearrangement being done on the separate isomers. Scheme 4 . It was found that 3α-aminomethyl-5α-cholestan-3β-ol(7) gave only the A-homocholestan-4-one on nitrous deamination, and 3β-amino-methyl-5α-cholestan-3α-ol (9) gave A-homocholestan-4-one as the only

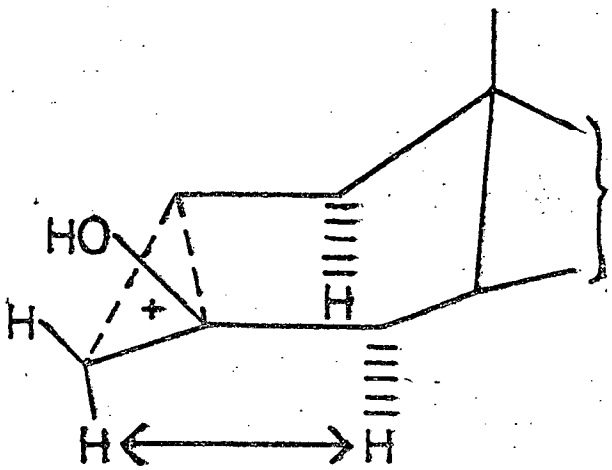
homologated ketone plus the expected exocyclic epoxide (17) in ratio 3:3:1. The results are summarised in Table 1. G.L.C. was used to separate the product mixture but no A-homo-3-one was found at retention time 2.70 expected relative to 5α-cholestane.

Compounds	Reagent	Products(%)				
		Oxiran	A-Homo-3-ketone	A-Homo-4-ketone	Ratio (3-CO)/(4CO)	Ref.
5α-cholestane series						
3α-CH_2NH_2(ax)-3β OH(eq)	HNO_2	Ca.0	Ca.0	70	small	(9)
3β-CH_2NH_2(eq)-3α OH(ax)	HNO_2	15	0	70	small	(9)
3β-CH_2NH_2(eq)-3α-OH(ax)	HNO_2	-	-	major product	small	(5)
3-ketone	CH_2N_2	-	10	40-50	Ca.0.2	(5)
17β-hydroxy-5α-androstane series						
3α-CH_2NH_2(ax)-3β-OH(eq)	HNO_2	very little	44	51	0.86	(6)
3β-CH_2NH_2(eq)-3α-OH(ax)	HNO_2	very little	47	33	1.4	(6)
3-ketone	CH_2N_2	very little	44	31	1.4	(6)

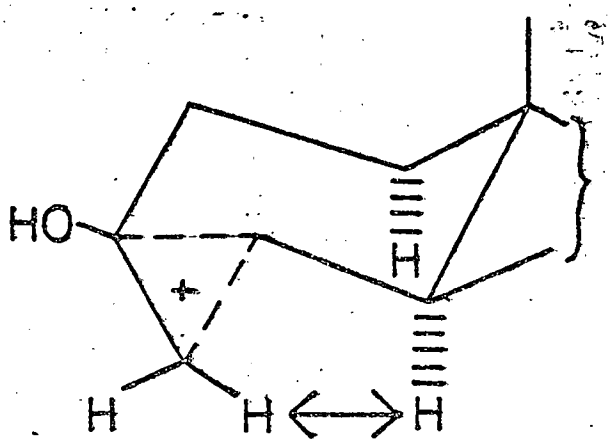
Table 1

Carlson and Behn[11] tried to explain the apparent total preference for C-2 migration to C-4 migration in the cholostane series by putting forward the idea that transannular hydrogen interactions

similar to those illustrated were the cause, since it was not obvious to them from consideration of Dreiding models why there should be a preferred conformation of either epimer of aminomethyl-alcohols (7) and (9) during the inversion of configuration at the migration terminus which accompanies carbon migration in the deamination of aminoalcohols.



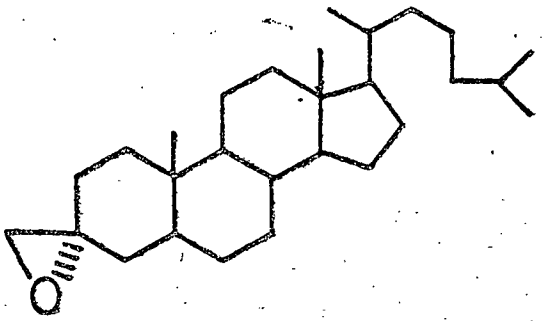
[15]



[16]

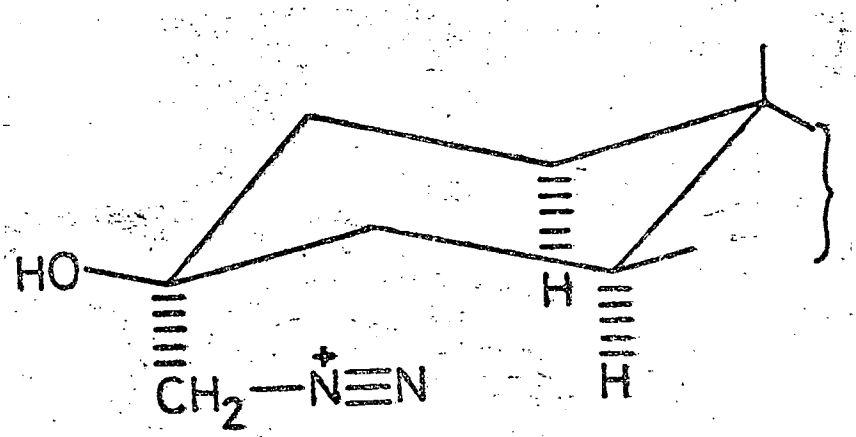
The interactions in transition state for C-4 migration (16) are certainly more severe than in the transition state for C-2 migration (15), so with dihedral angular distortion and non-bonded interactions this partially explained the results. Only partially however, since 17β-hydroxy-androstan-3-one (2) has formed both ring homologated ketones (12) and (14) on nitrous deamination of the corresponding 3-aminomethyl-androstan-3-ols. This left the little understood long range effects as the only probable answer. The same arguement was used for the deamination of the epimeric 3β-aminomethyl-cholestan-3α-ol (9), the presence of epoxide by-product (17) from only

this epimer being in line with other work showing more epoxide always resulting from the epimer with equatorial aminomethyl group.



[17]

The unfavourable hydrogen interactions between the 3-axial diazonium methyl group and the C-1α and C-5α hydrogens in the transition state (18) which would have led to epoxide formation from the α-amino-methyl-β-alcohol (7), completely hinders the reaction. No such interactions are present however in the case of the β-aminomethyl-α-alcohol (13) allowing epoxide formation to take place. Jones and Zander[12] and Jones and Price[13], in separate work appear to show that this long range electrical effect is unique to the C_8H_{17} cholestane C-17β side chain in its influence on the product ratios in ring-A homologation reactions.

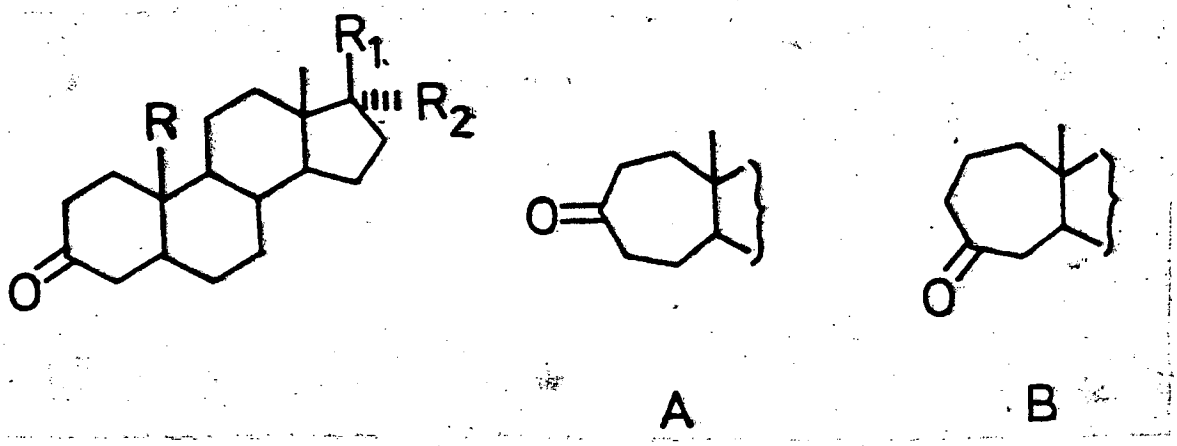


[18]

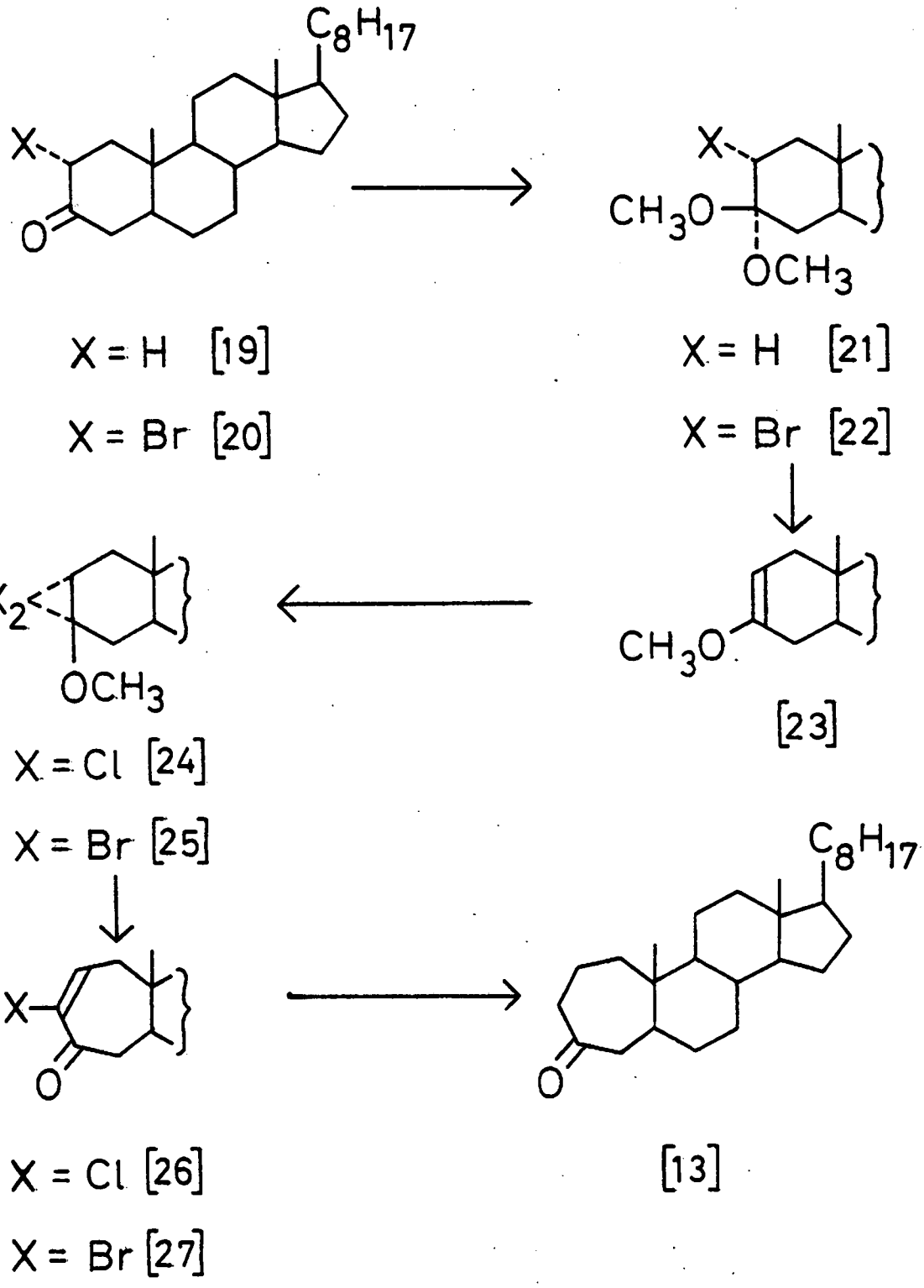
Their work with the diazomethane reaction[14] consisted of changing the C-17 substituents and the use of the 5-β series as well as 5-α. Their results are summarised in Table 2.

	R	R_1	R_2	Ratio B:A±3%
5α	CH_3	OH	H	41:39
5α	CH_3	H	OH	45:55
5α	CH_3	H	H	42:58
5α	CH_3	OAc	H	45:55
5α	CH_3	OH	CH_3	38:62
5α	CH_3	C_8H_{17}	H	79:21
5α	H	OH	H	40:60
5α	H	OAc	H	45:55
5β	CH_3	C_8H_{17}	H	22:78
5β	CH_3	OH	H	50:50
5β	H	OH	H	39:61

Table 2



In 1969, Levisalles et al.[15,16] set out to prepare A-homo-cholestan-4-one by a completely unambiguous route for circular dichroism and rotary dispersion studies. This involved generation of a dihalogenated carbene by the method of Doering and Hoffmann[17] by


C8H17
X
O
X = H [19]
X = Br [20]
X
CH3O
OCH3
X = H [21]
X = Br [22]
CH3O
[23]
X2
OCH3
X = Cl [24]
X = Br [25]
X
O
X = Cl [26]
X = Br [27]
C8H17
O
[13]

Scheme 5

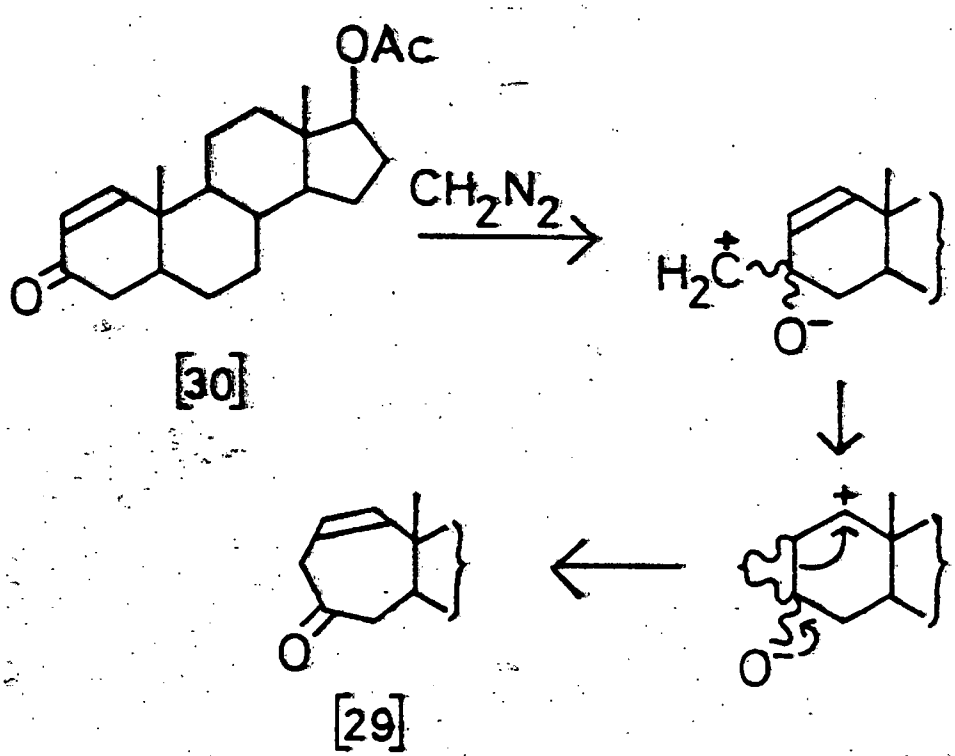
treating a haloform with a strong base. In this case chloroform and potassium tertiarybutylate were used giving a dichlorocarbene which was added to 3-methoxy-5α-cholest-2-ene (23). The cyclopropane derivative (24) was hydrolysed in aqueous acetic acid in the presence of silver acetate to the halogenated enones (26). Hydrogenation in the presence of palladium/charcoal (5%) and sodium carbonate gave A-homo-5α-cholestan-4-one. Scheme 5 . The position of the double bond in the substrate for carbene addition (23) was fixed by the preparation of the same compound from the known 2α-bromo-5α-cholestan-3-one (20) via the ketal (22). The reactions were also carried out using bromoform to form the corresponding cyclopropane adduct (25) and halogenated enone (27). The stereochemistry of the carbene addition was assigned in accord with usual methods of attack on 5α-cholest-2-ene derivatives however it is without influence on the following stage. A-homo-5α-cholestan-3-one was prepared by the unambiguous route of Stork et.al.[18] and the products of these reactions, nitrous deamination and diazomethane ring expansions, studied by optical rotary dispersion and circular dichroism.

Product	Mode of Preparation	M.P.	$[\alpha]_D^{\circ}$	O.R.D. amplitude	CD	
					MAX	MAX
(11)	By Stork et al.[18]	83-85°C	+43	-81(D) -97(M)	296.5 285	-1.43(D) -1.91(M)
	CH_2N_2on(1)	82.83°C	+50	-60(M)		
(12)	CH_2N_2on ketone (2)			-87(D₃H) -98(M)		
(13)	CBr_2 on (23)	96-97.5°C	+103	+130(D) +149(M)	294 286	+2.56(D) +3.26(M)
	Nitrous deamination of (7) & (9)	85-87°C	+50	+15(D)		
	CH_2N_2on (1)	87-88°C	+31	+15(M) +14(M)		+0.41(D) +0.42(I)
		85-87	+50	+32(D) +159(M)	294	+2.84(D)
(14) (28)	CH_2N_2 CH_2N_2,$AlCl_3$ on (30)				294	+2.67(D)

D = Dioxan H = Hexane I = Iso-octane M = Methanol

Table 3

The corresponding homologated androstanes were also prepared, the structure of the A-homo-4-one (28) being fixed by preparation from 17β-acetoxy-androst-1-en-3-one (30) by reaction with diazomethane Scheme 6 and hydrogenation of the ring-A expanded product (29). The results brought Levisalles and his co-workers to the conclusion that the previous ring-A homologated ketones, thought to have been only A-homo-5α-cholestan-4-one by Tiffeneau-Demjanov rearrangement, were in fact mixtures of this and the A-homo-3-one which show the same infra-red and mass spectra, and their retention times in gas chromatography are the same and so these techniques do not distinguish between the ketones leaving optical rotary dispersion, and circular dichroism as the preferred means of identification. From comparison



Scheme 6

of the optical rotary dispersion and circular dichroism curves of pure homologated ketones, they were able to calculate the percentage yields of each ketone in the mixtures finding that diazomethane afforded 43±5% of A-homocholestan-4-one and 57±5% of A-homocholestan-3-one, while nitrous deamination gave 50±5% of each ketone.

A recent paper by Jones and Price[19] repeated the optical rotary dispersion study. They again found the ring-A homologated ketone of cholestane to be present after the Tiffeneau-Demjanov rearrangement but that the product ratios were significantly different from deamination of the epimeric aminomethyl alcohols (7) and (9). They also found a predominance of equatorial attack by diazomethane, the rearrangement products being similar to those for β-aminomethyl-5α-cholestan-3α-ol (9). They concluded that no long range effects need be invoked since there was in fact no predominace of either C-3, 4 or C-2,3 bond migration but that the argument for epoxide formation still held. Their results are summarised in Table 4.

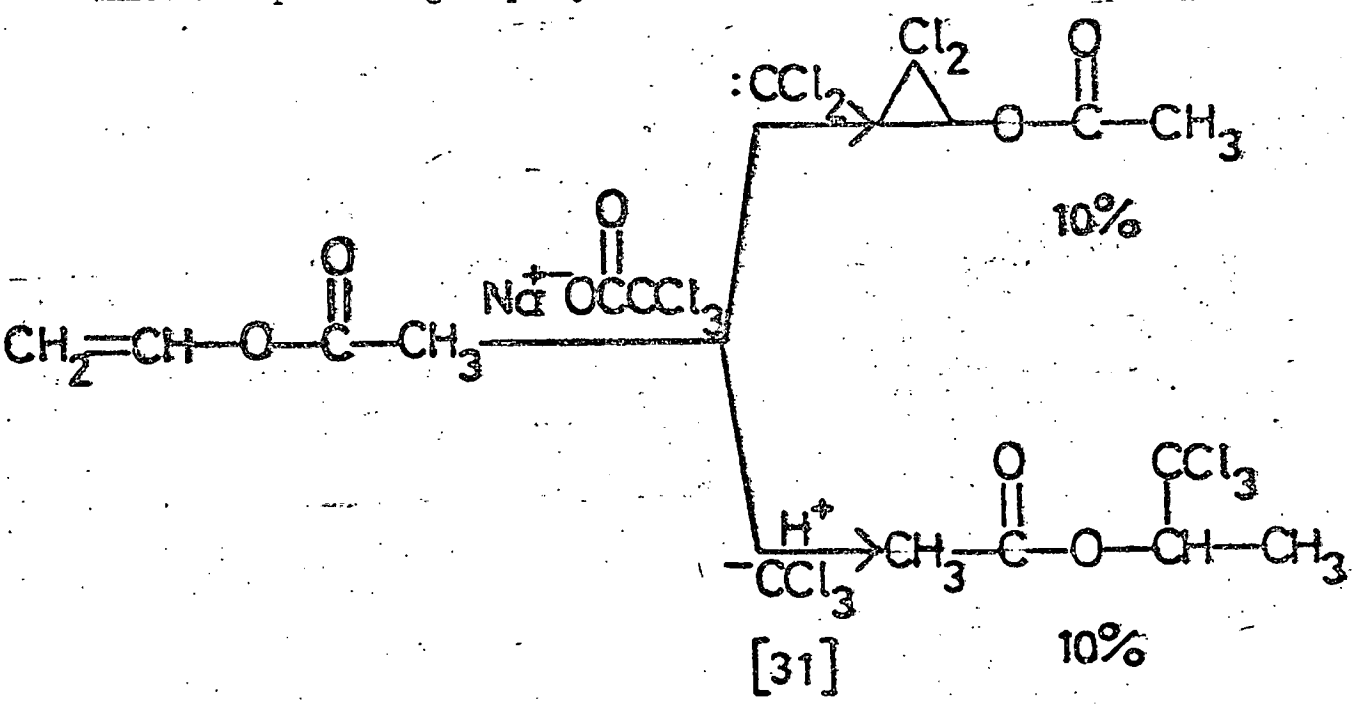
Starting Material	Method of homologation	% yield 11+13 or 12+14	Mol.amp 11+13 or 12+14	% ratio 11:13 12:14
8	Tiffeneau-Demjanov	95(-1)	+32.2	49.5:50.5
10	Tiffeneau-Demjanov	80(-8)	+ 1.6	61.5:38.5
2	Diazomethane	75(-7)	+ 9.0	59:41
7	Tiffeneau-Demjanov	88(-5)	+32.0	48:52
9	Tiffeneau-Demjanov	73(-15)	- 6.3	63:37
1	Diazomethane	80(-13)	+ 5.2	58.5:41.5

Table 4

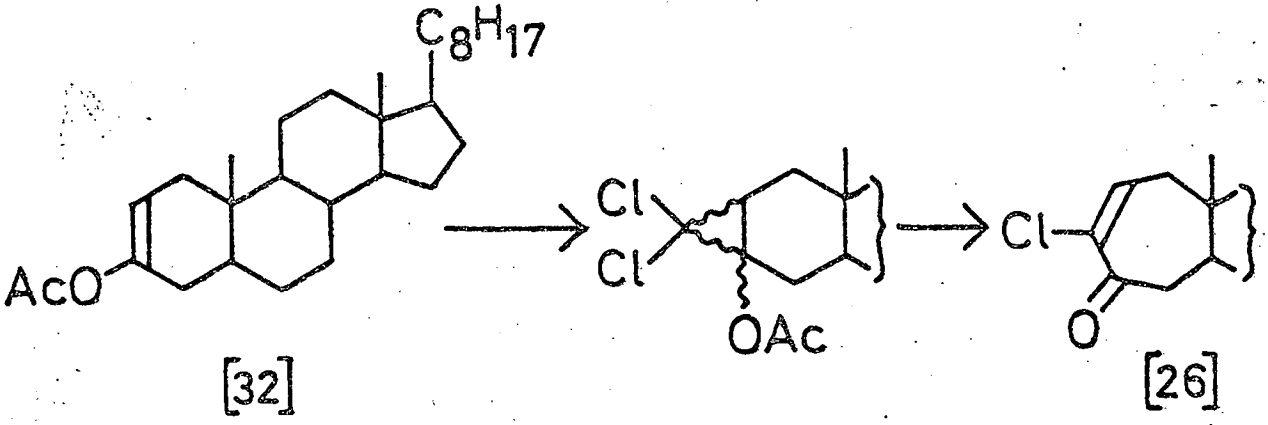
The O.R.D. spectra were run in methanol.

Values in parenthesis are % yields (G.L.C.) of C-3 oxiran products.

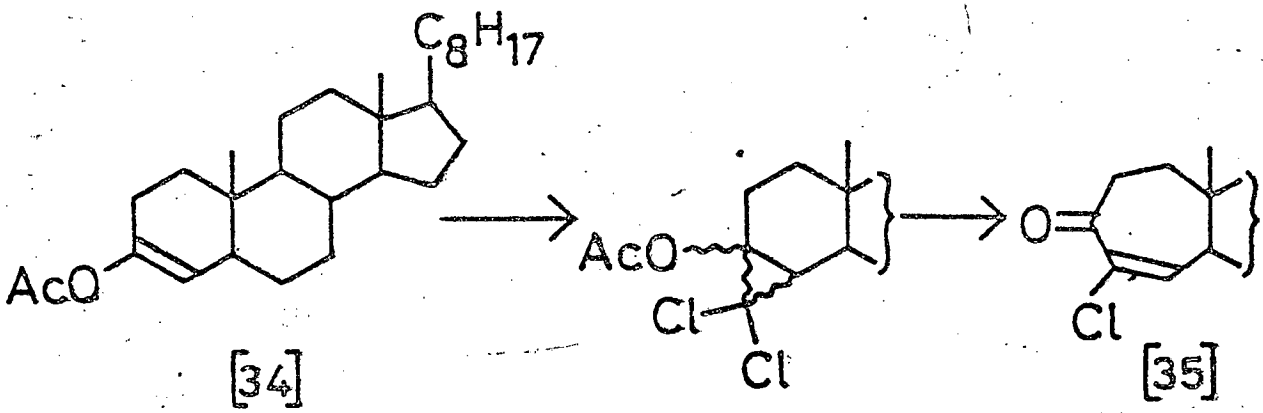
The method of Stork et al.[18] used by Levisalles and co-workers involved the generation of carbene from a phenyl mercuric precursor. The Doering-Hoffmann generation of carbenes[20,21,22] is limited to additions on substrates having no base-sensitive groups. Enol acetates are readily accessible compounds but would require neutral conditions. Wagner et al.[23] in 1961 generated dihalocarbenes by thermal decomposition of sodium trichloroacetate[24]. Although this afforded the required neutral conditions, it was found to give poor yields with weakly neucleophilic olefins, a side reaction between the carbene and trihaloacetate intercepting much of the carbene. Another major disadvantage, found in the Doering-Hoffmann method also, was the reaction of the intermediate trihalomethide ion (31) with some substrates before it can decompose to dihalocarbene. Scheme 7 . Seyferth et al.[25a] underwent a study of phenyl (trihalomethyl) mercuric compounds similar to species found by Russian workers[26], which decomposed to give phenylmercurichalide in high yield.



Scheme 7



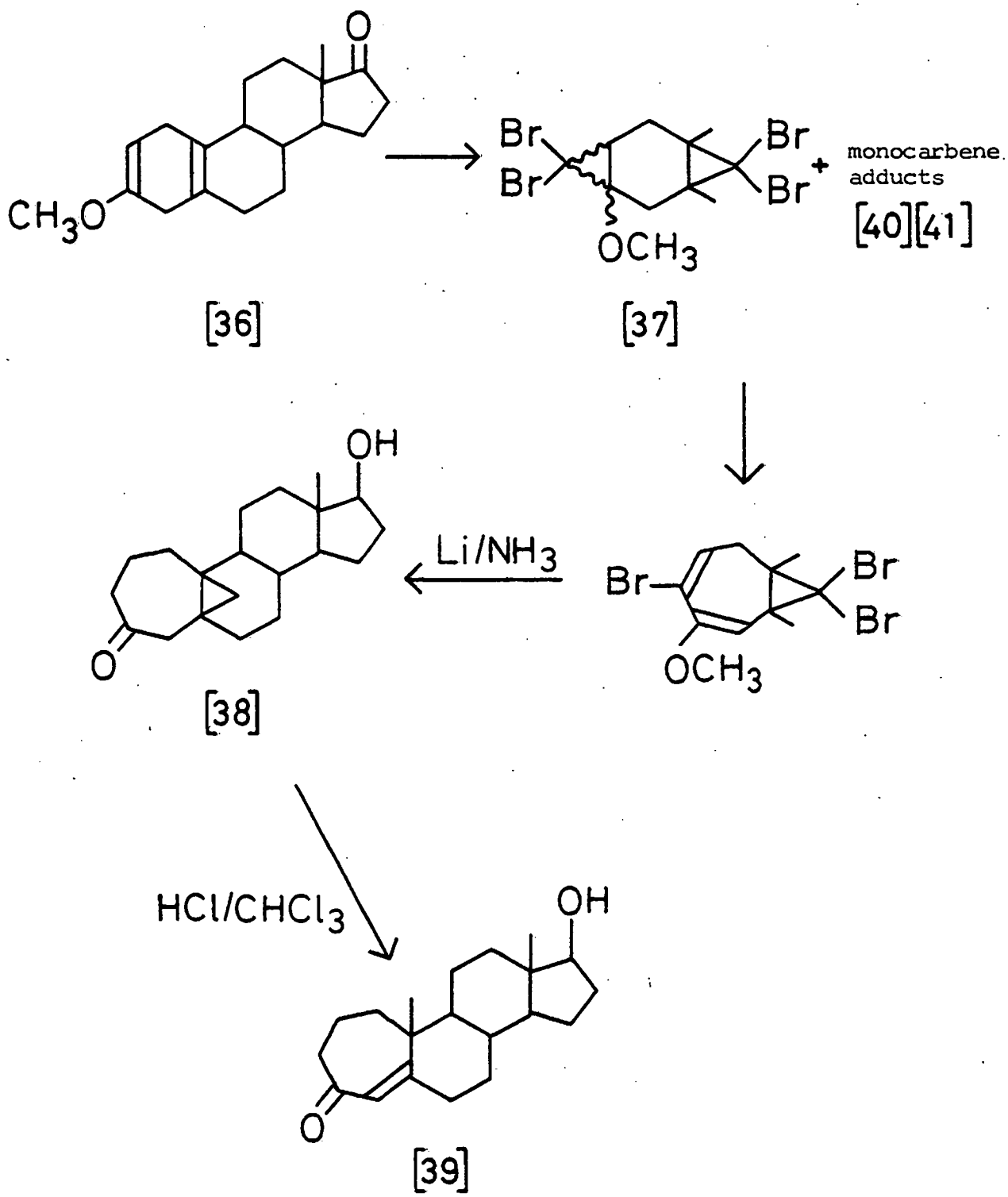
[32] [26]



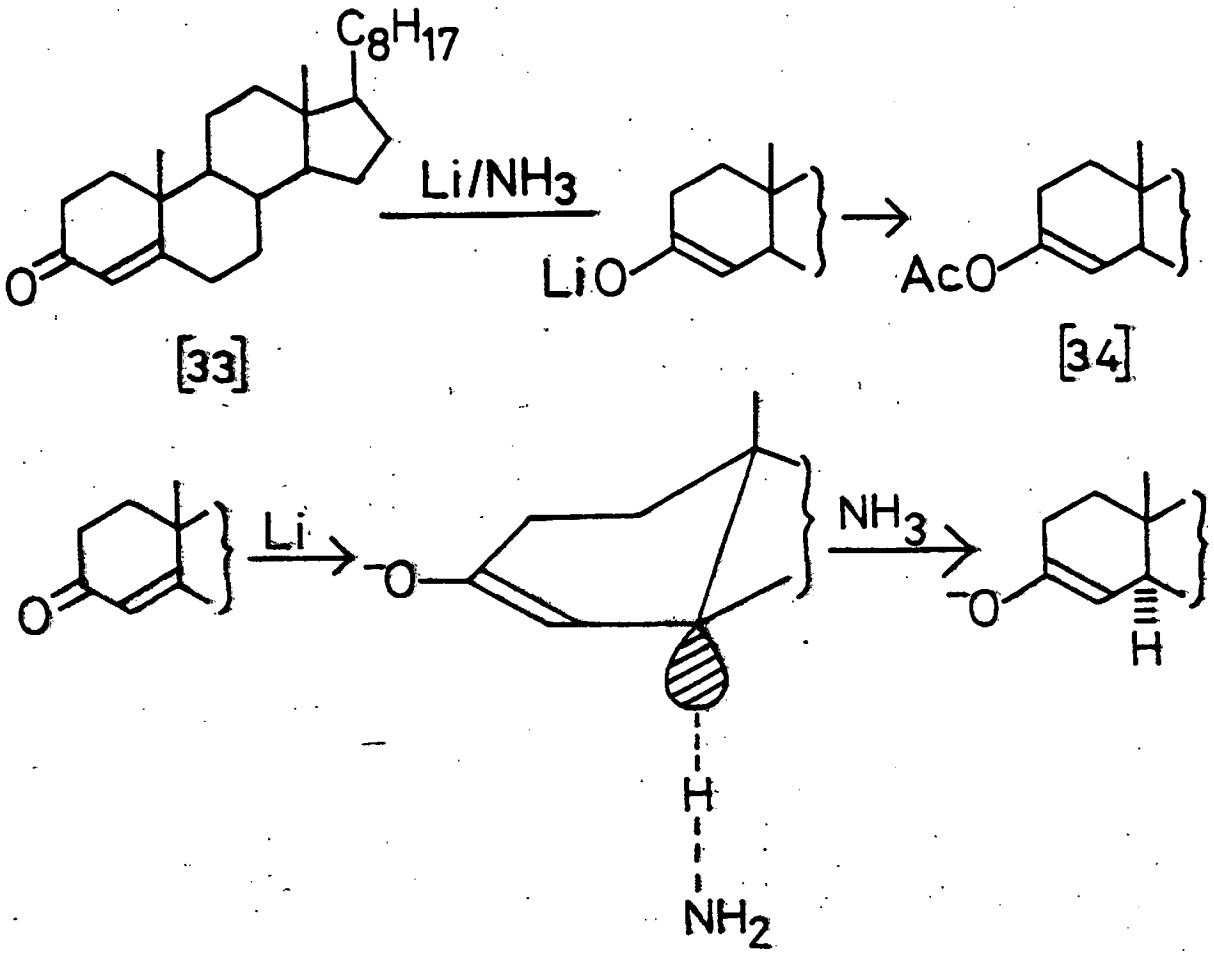
[34] [35]

Scheme 8

They found these compounds to decompose at 150°C or in ethanolic solution via a carbene intermediate which could be trapped by olefinic speces. Fifty substrates were tested[25b], most of which gave high yields of cyclopropane derivatives. Further work by Seyferth and co-workers[27a-g] led to a convenient method for carbene generation by decomposition of various phenyl (trihalomethyl) mercury compounds under neutral conditions. One such phenylmercuric compound, phenyl (dichlorobromomethyl) mercury was the precursor used by Stork et al.[18], giving high yields of carbene addition products from enol acetates of cholestan-3-one. These rearranged under basic conditions to 4-chloro-A-homo-5α-cholest-4-en-3-one (35) and 3-chloro-A-homo-5α-cholest-2-en-4-one (26) from 3-acetoxy-5α-cholest-3-ene (34) and 3-acetoxy-5α-cholest-2-ene (32) respectively. Scheme 8 . The enol acetate (34) used by Levisalles and co-workers is less stable than the corresponding enol acetate (32) used for A-homo-4-ketone preparation and does not form in the enol acetylation of 5α-cholestan-3-one. Stork and co-workers[28], however, developed a specific enolate synthesis involving reaction of the unsaturated ketone (33) with lithium-liquid ammonia, followed by treatment of the resulting lithium enolate with acetic anhydride. Scheme 9 . This gave a method for synthesis of previously unattainable enol acetates and so widened the scope of carbene substrates.

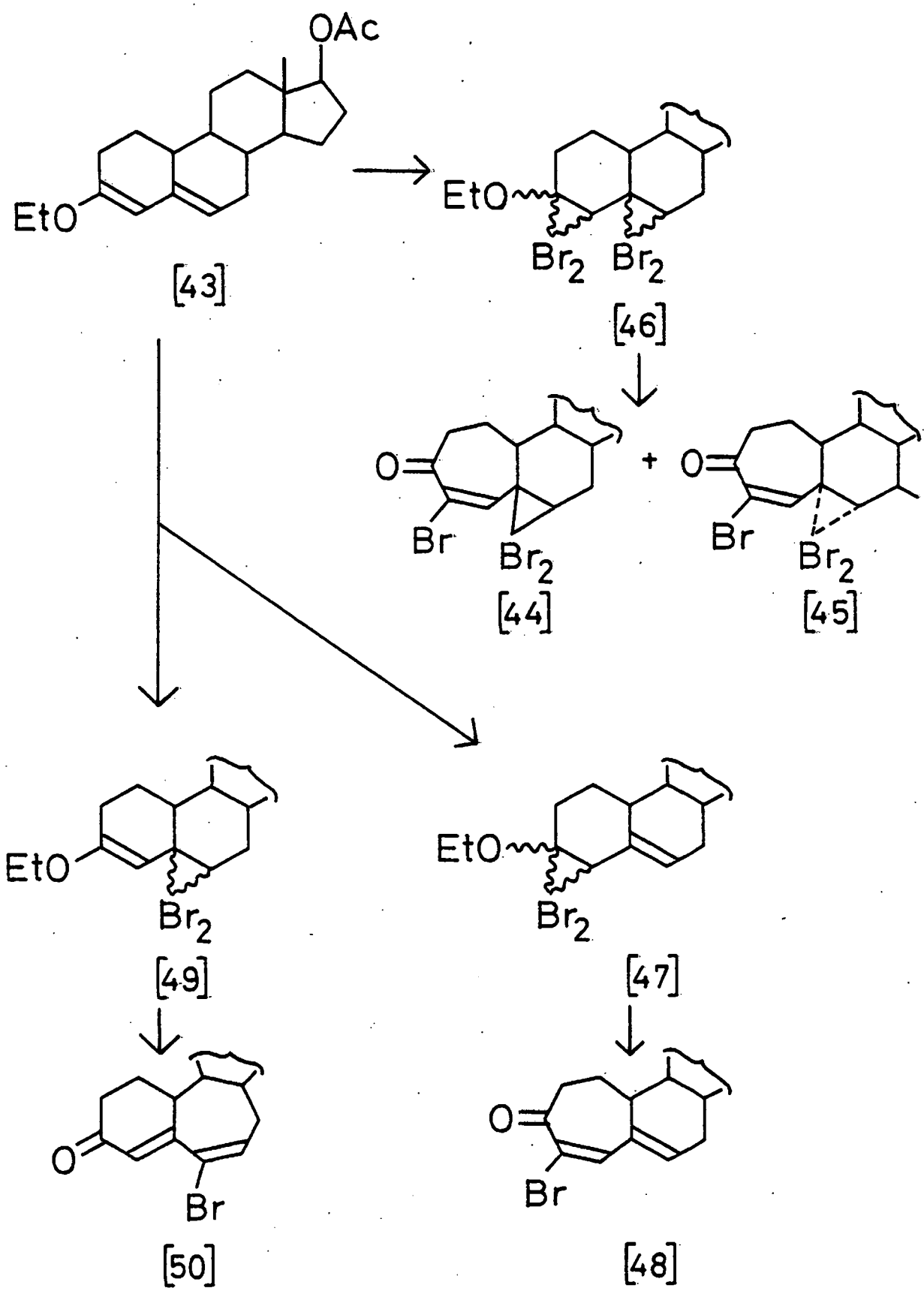

O
CH3O
Br
Br
Br
Br
OCH3
monocarbene
adducts
[40][41]
[36]
[37]
OH
Li/NH3
Br
Br
Br
OCH3
O
[38]
HCl/CHCl3
OH
O
[39]

Scheme 10



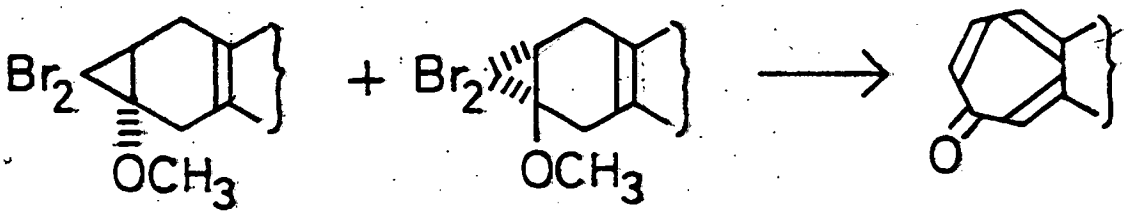
Scheme 9

The Doering and Hoffmann method, and the Wagner method still found use however in the preparation of A-homosteroids. Birch and Subba Rao[29] prepared the first reported α,β-unsaturated ring-A expanded ketone, A-homotestosterone (39) Scheme 10 by addition of dibromocarbene made from potassium tertiarybutoxide and bromoform, to 3-methoxy-19-nor-androsta-2,5(10)-dien-17-one (36). The dicarbene addition products (37) were rearranged in pyridine, reduced with lithium-liquid ammonia to give the saturated ring-A expanded species (38) containing a methylene bridge. Rearrangement with hydrogen chloride in chloroform gave the required A-homotestosterone. The monocarbene addition products also formed during the reaction (40) and (41) rearrange


OAc
EtO
[43]
EtO
Br2 Br2
[46]
O
Br
Br2
[44]
+
O
Br
Br2
[45]
EtO
Br2
[49]
EtO
Br2
[47]
O
Br
[50]
O
Br
[48]

Scheme 12

as the 17-ketals to the bromine free ring-A expanded unsaturated ketone (42) probably due to loss of hydrogen bromide involving an initial shift of a double bond by enolisation Scheme 11 .

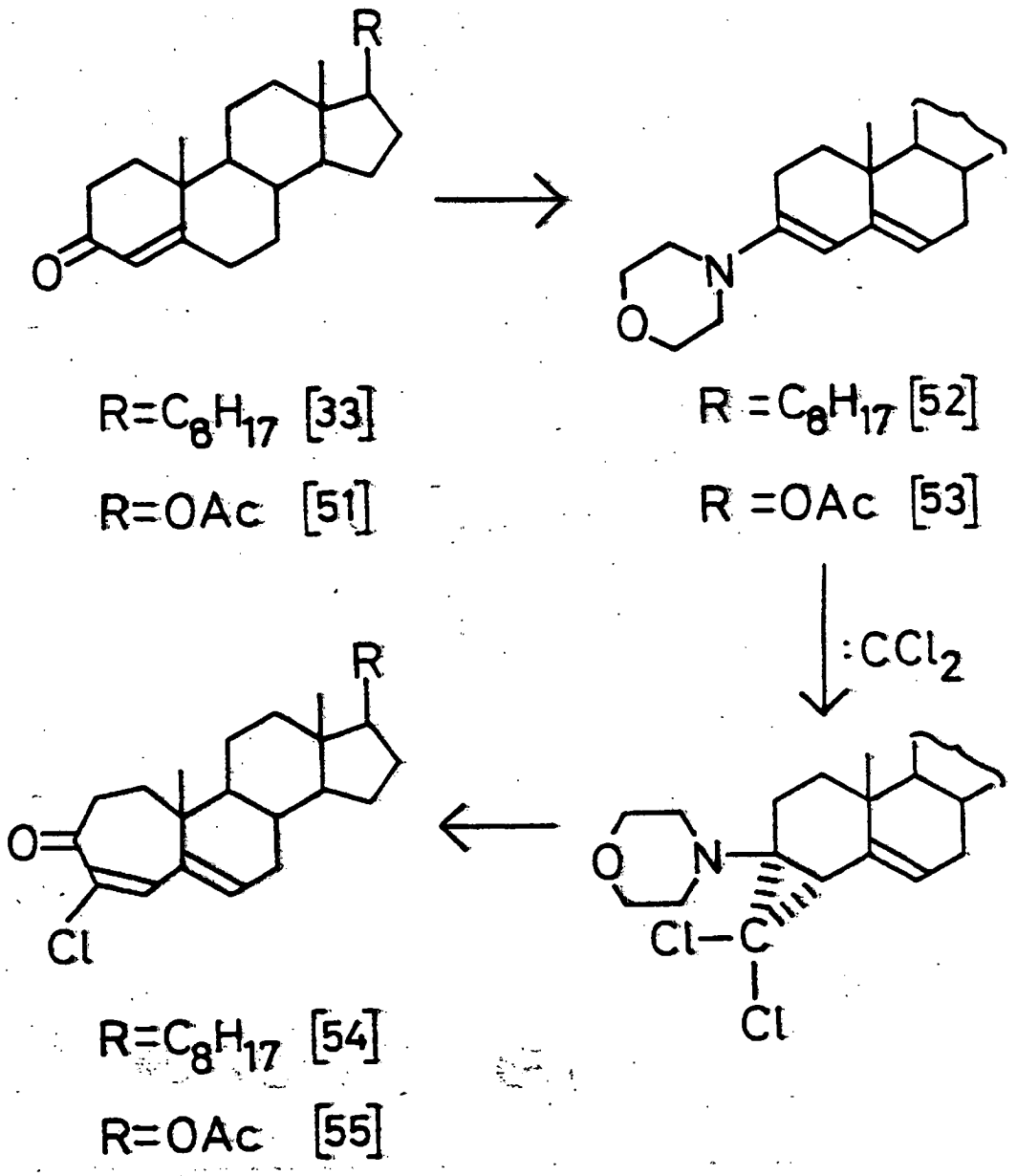


[40] [41] [42]

Scheme 11

Font[30], in 1964, used the same method to add carbenes to 17β-acetoxy-3-ethoxy-oestra-3,5-diene (43). He found he could prepare two brominated A-homo types, a tri-bromo product (44) and its epimer (45), and a mono-bromo product (48) arising from the di-carbene addition and mono-carbene addition products respectively (46) and (47). This was contrary to the 19-nor-Δ-3,5 steroids which react with dihalocarbene exclusively from the β-face[35], and the dehydroestrone methyl ethers whose enolic double bond is the most reactive. Here, the carbene adds both α and β to the 5,6-double bond, the yields of A-ring homologues being low due to preferred mono-carbene addition to the 5,6-double bond leading to a ring-B expanded mono-bromo product (50).

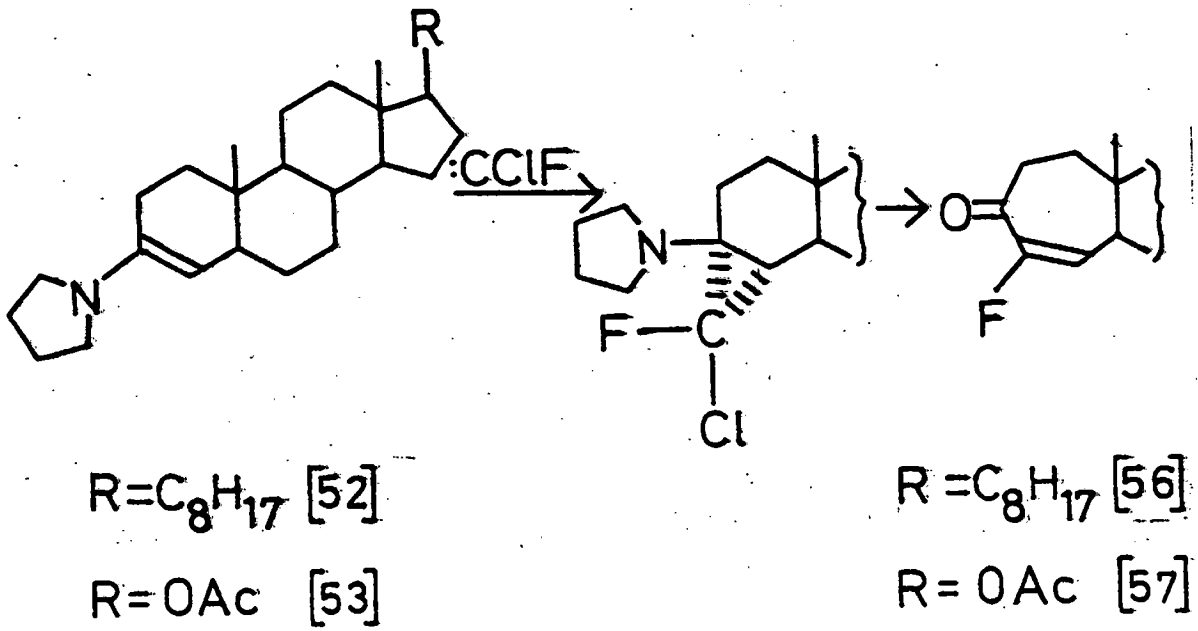
The Wagner carbene generation method was employed by Pandit and de Graaf[31] in the preparation of 4-chloro-A-homo-cholesta-4,5-dien-3-one (54) and the corresponding androstane (55) Scheme 13 .



Scheme 13

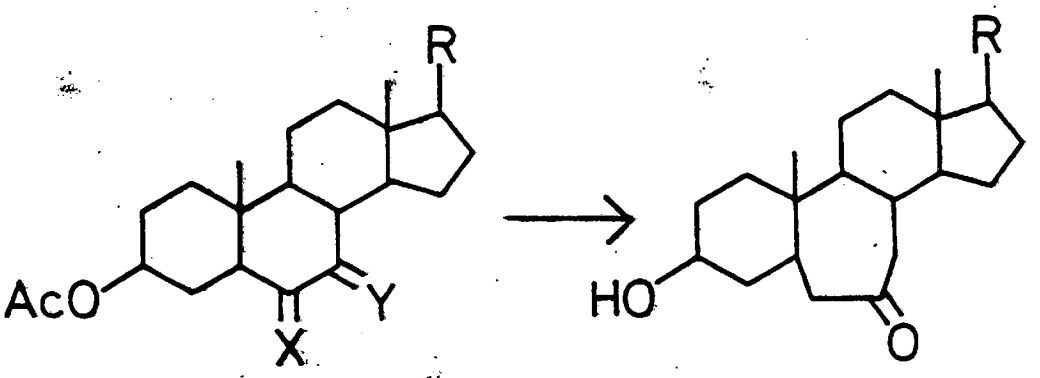
Carbene addition to the morpholidine enamines (52)(53) and rearrangement with water gave the cholestane and androstane ring-A expanded products (54)(55) in 31% and 34% yields respectively. A recent paper by the same authors[32] studying the role played by the "morpholidine" nitrogen in lowering the energy of the transition state of the ring opening process, furthered their previous work by catalytically reducing the ring expanded diene (48) to form the known A-homocholestan-3-one (11), and by

preparing A-homo-4-fluoro-steroids (56)(57) by rearrangement of the addition products of choloro-fluorocarbene to the pyrrolidine enamines (52)(53). Scheme 14 . No mono-chloro-A-homo steroids were produced. The generation of chlorofluorocarbene was from a phenylmercuric precursor, phenyl (dichlorofluoromethyl) mercury.[35]



Scheme 14

The B-homosteroid structure prepared in the work by Pandit and de Graaf was first prepared, in the androstane series by Ringold[33] in 1960, by Tiffeneau-Demjanov rearrangement of 7-aminomethyl-7-alcohols prepared in the same manner as the corresponding 3-aminomethyl-3-alcohols (8)(10). Ringold was unable to say whether he had prepared the B-homoandrostan-7-one (61) or the corresponding -7a-one (65) or what the configuration at C-8 was. Himitsu[34] in 1961 prepared the same B-homo-ketone from both cholestan-6-one (58) and cholestan-7-one (62) showing the configuration to be 5α and 8β and the carbonyl at position C-7. Scheme 15 . Sorm et al.[37] in fact prepared 3β-acetoxy-B-homo-cholestan-7a-one (64) by reaction of diazomethane with 3β-acetoxy-cholest-5-en-7-one (63) followed by hydrogenation. Scheme 16 .



$R=C_8H_{17}; X=O; Y=H_2$ [58] $R=C_8H_{17}$ [60]

$R=OAc; X=H_2; Y=O$ [59] $R=OH$ [61]

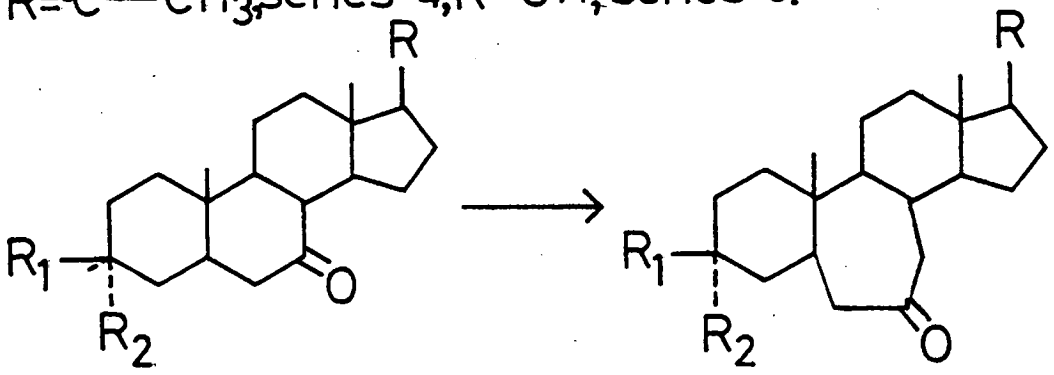
$R=C_8H_{17}; X=H_2; Y=O$ [62]

Scheme 15

Further work by Ringold[36], Sorm and co-workers[37] and Japanese workers[38] led to a whole series of B-homo-steroids by modification of the original homologated parent ketones prepared from the Tiffeneau-Demjanov rearrangement. Scheme 17 . Ringold found that the change from a six-carbon B-ring to a seven-carbon B-ring did not significantly influence androgenic or mytrophic activity. The A-ring is hardly distorted although the B- and C-rings are, affecting the enzyme "fit" in the centre of the molecule.

R=-CH(OAc)-CH$_3$, series 1; R=C_8H_{17}, series 2; R=OAc, series 3;

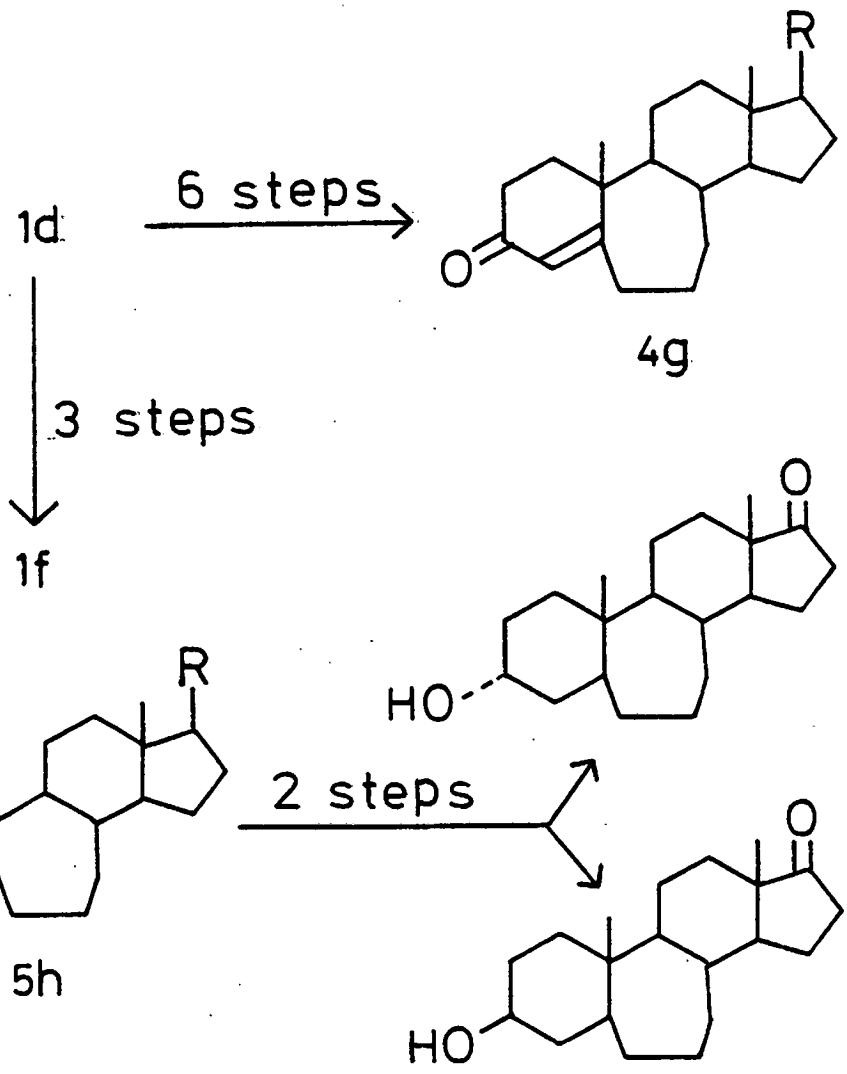
R=-C(=O)-CH$_3$, series 4; R=OH, series 5.

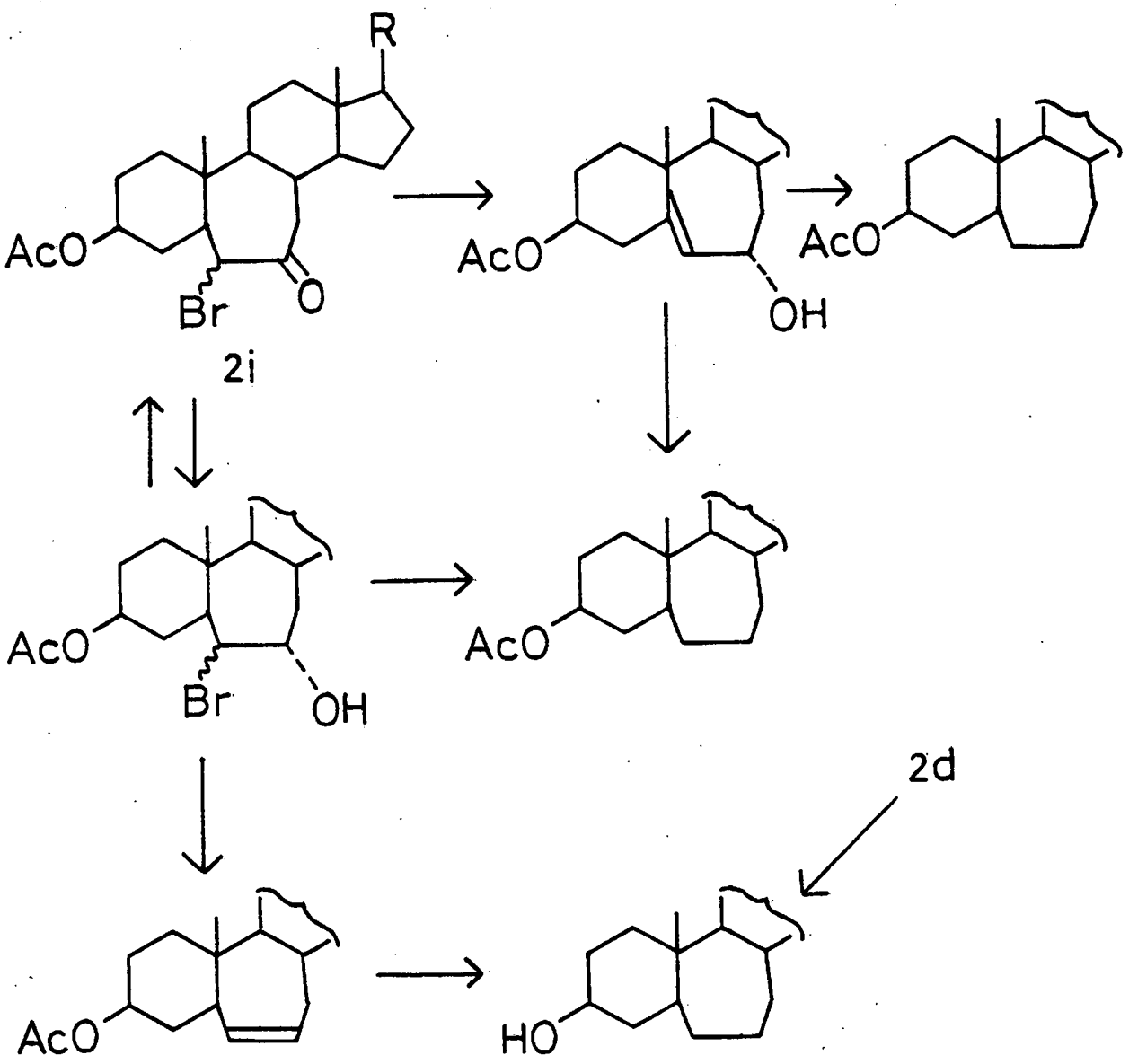


R_1=H, R_2=OAc 1a, 2a, 3a. R_1=H, R_2=OAc 1b, 2b, 3b.

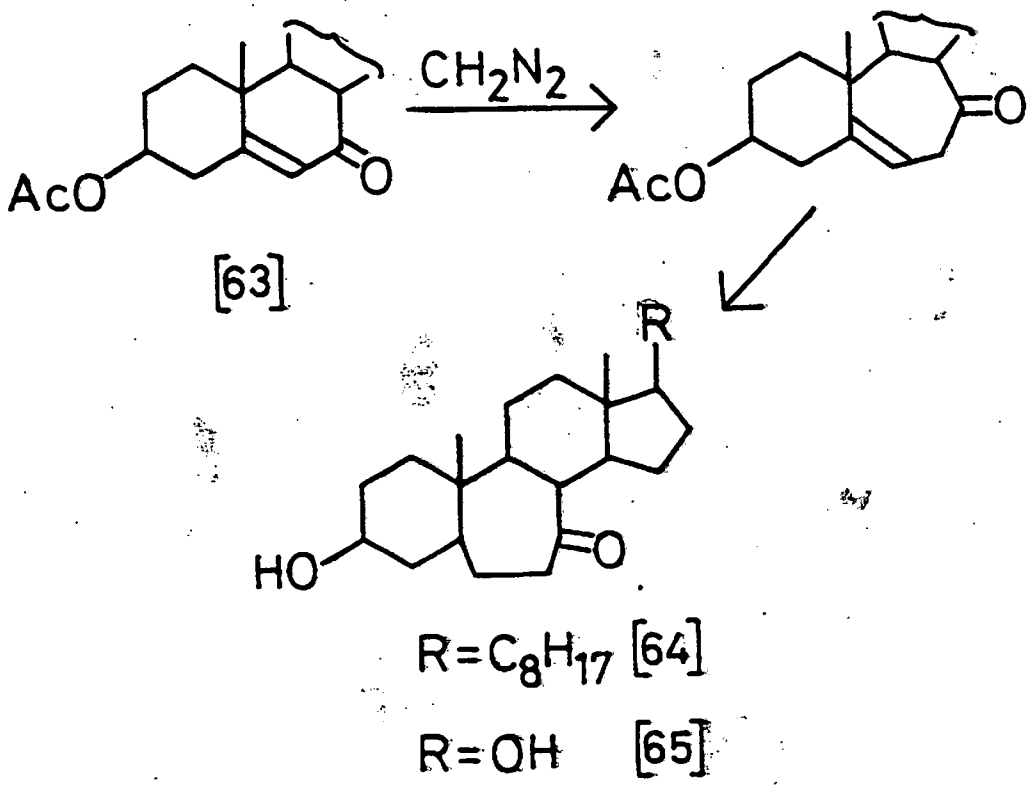
R_1=OAc, R_2=H 1c, 2c, 3c. R_1=OAc, R_2=H 1d, 2d, 3d.

R_1, R_2=H 1e, 2e, 3e. R_1, R_2=H 1f, 2f, 3f.



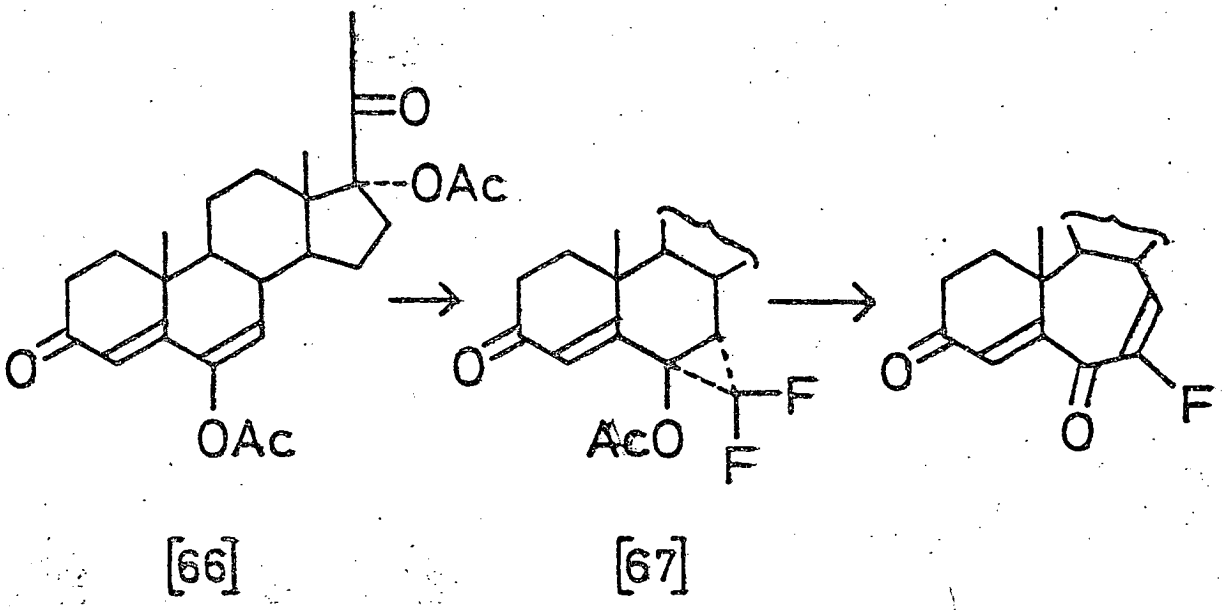


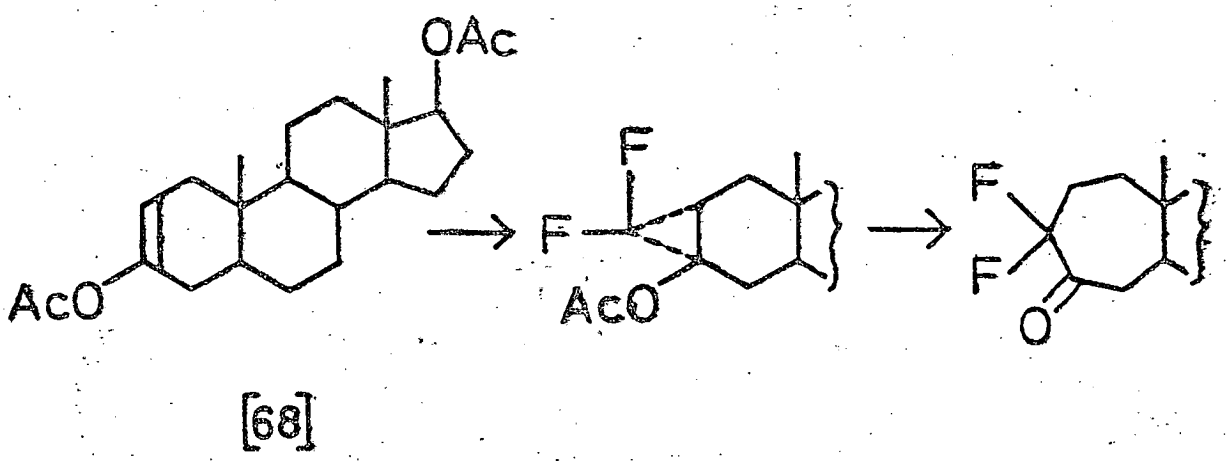
Scheme 17



Scheme 16

Ring-B expansion by diflourocarbene addition to an enol acetate has been carried out by Crabbe et al.[39] and was shown to be different from the corresponding ring-A expansion since the cyclopropane derivative(67) from 6,17α-diacetoxy-pregna-4,6-dien-3-one (66) rearranges with base to give a mono-fluoro ring-expanded species whilst a difluoro-ring-A homologated adduct results from the rearrangement of the corresponding cyclopropane derivative of 3,17β-diacetoxy-androst-2-ene (68). Scheme 18 .

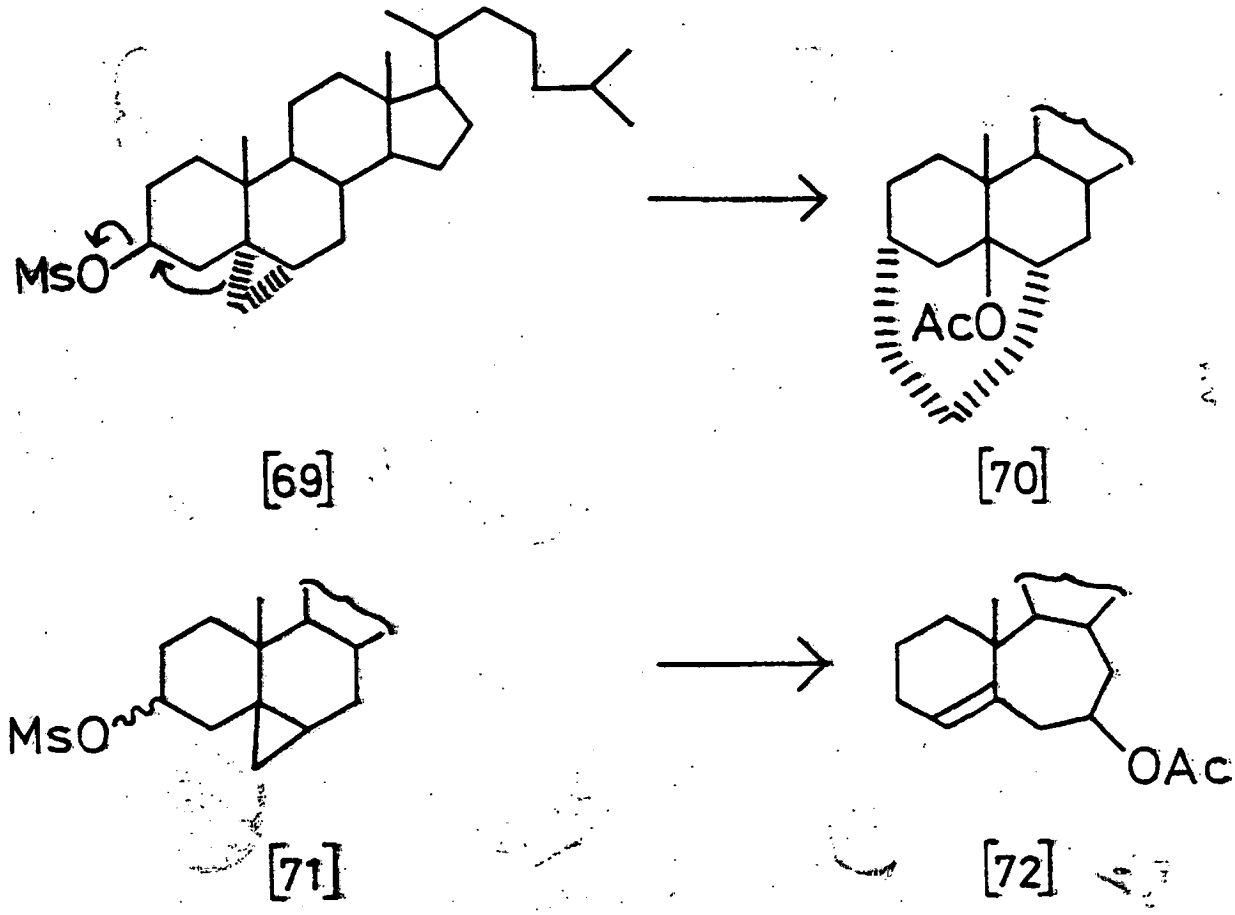




Scheme 18

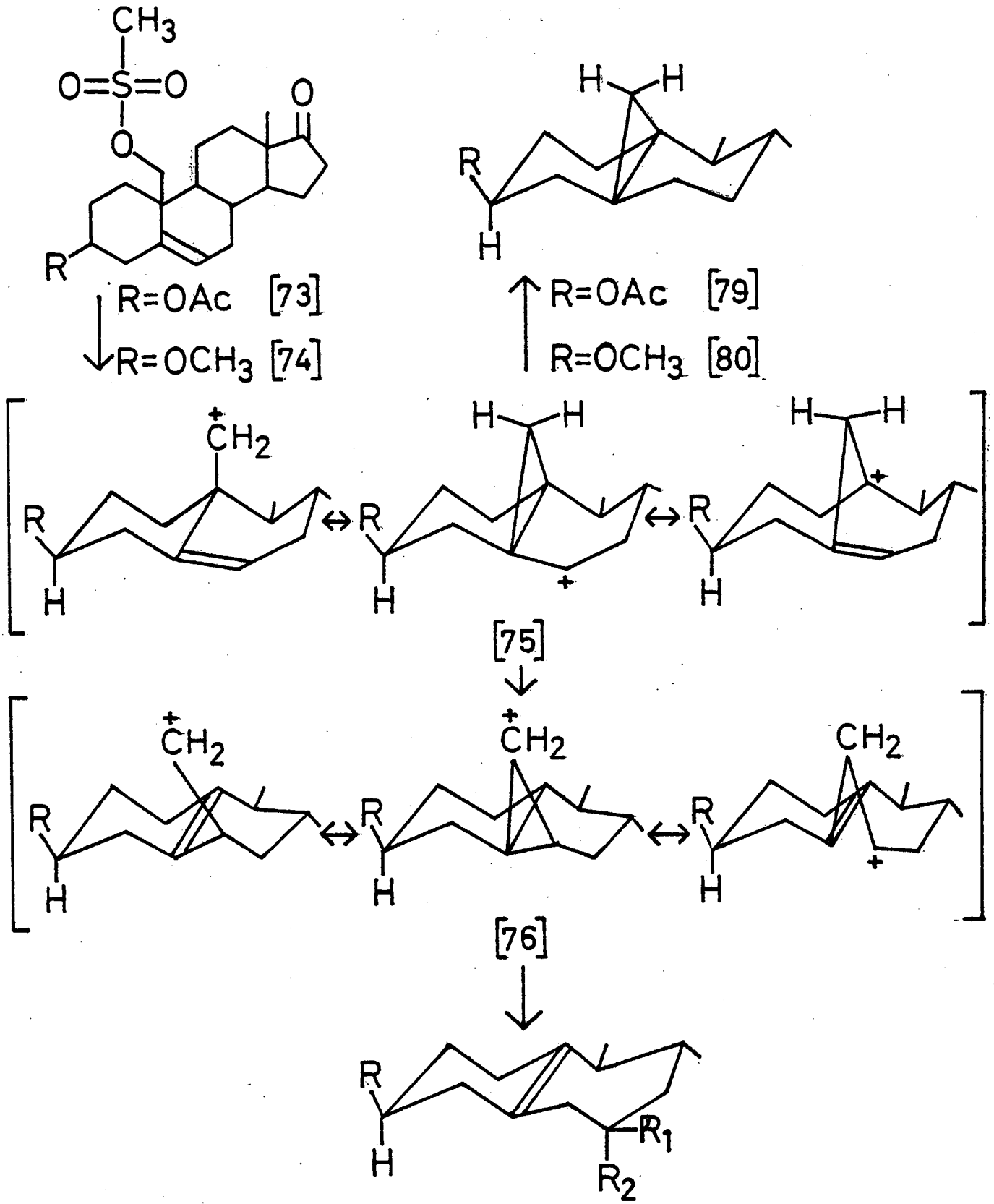
In the diene substrate(66), the difluorocarbene addition was exclusively to the 6,7-double-bond, rearranging in the classical manner to give the required B-homo compound as the only product.

Other B-ring homologations include work by Sorm et al. on the acetolysis of the mesylates of the 5,6-β-methano-3-alcohol derivative (71), found to give 7β-acetoxy-B-homocholest-4-ene (72). The α-methano (62) led to a 3,6-cyclo product (70). Scheme 19 .



Scheme 19

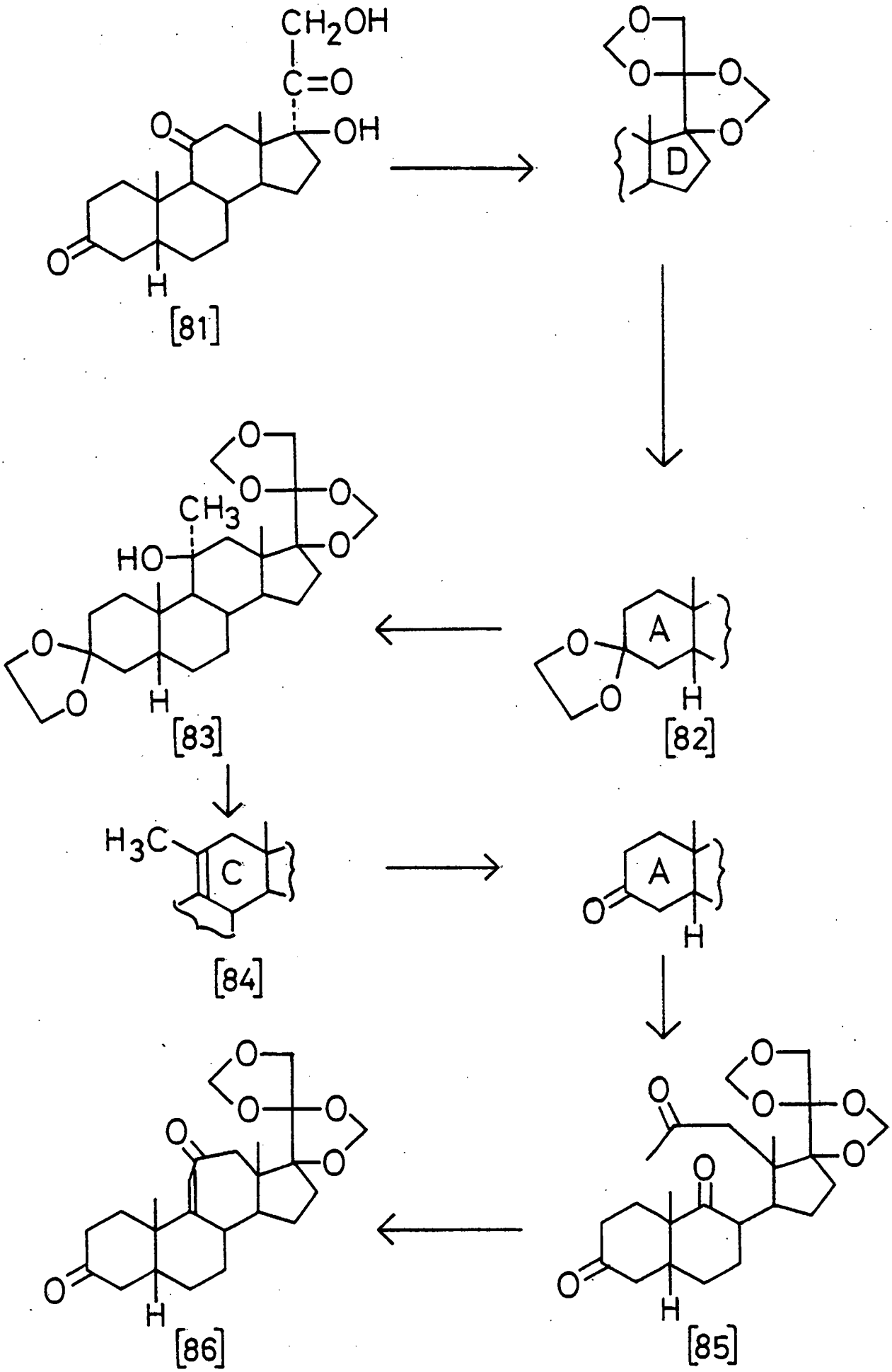
Tadanier[40], in 1966, studying the homoallylic rearrangements of 19-substituted steroids in elimination reactions and nucleophilic substitution reactions, found that the nature of the products requires the intervention of two discrete interconvertable homo-allylic cations, dependent on reaction conditions, one of which exists under kinetically controlled reaction conditions and the other during thermodynamic control. These intermediates can be stabilised by delocalisation of charge for which resonance forms can be written (75)(76), each leading to different products. Tadanier found, on treatment of 3β-methoxy-19-methanesulphonoxy-androst-5-en-17-one (74) with water and potassium acetate for sixteen hours in refluxing acetone,


CH3
O=S=O
O
O
R
R=OAc [73]
R=OCH3 [74]
H H
R
H
R=OAc [79]
R=OCH3 [80]
CH2
[75]
[76]
R1
R2
R=OAc; R1 or R2=F [77]
R=OCH3; R1=OH; R2=H [78]

Scheme 20

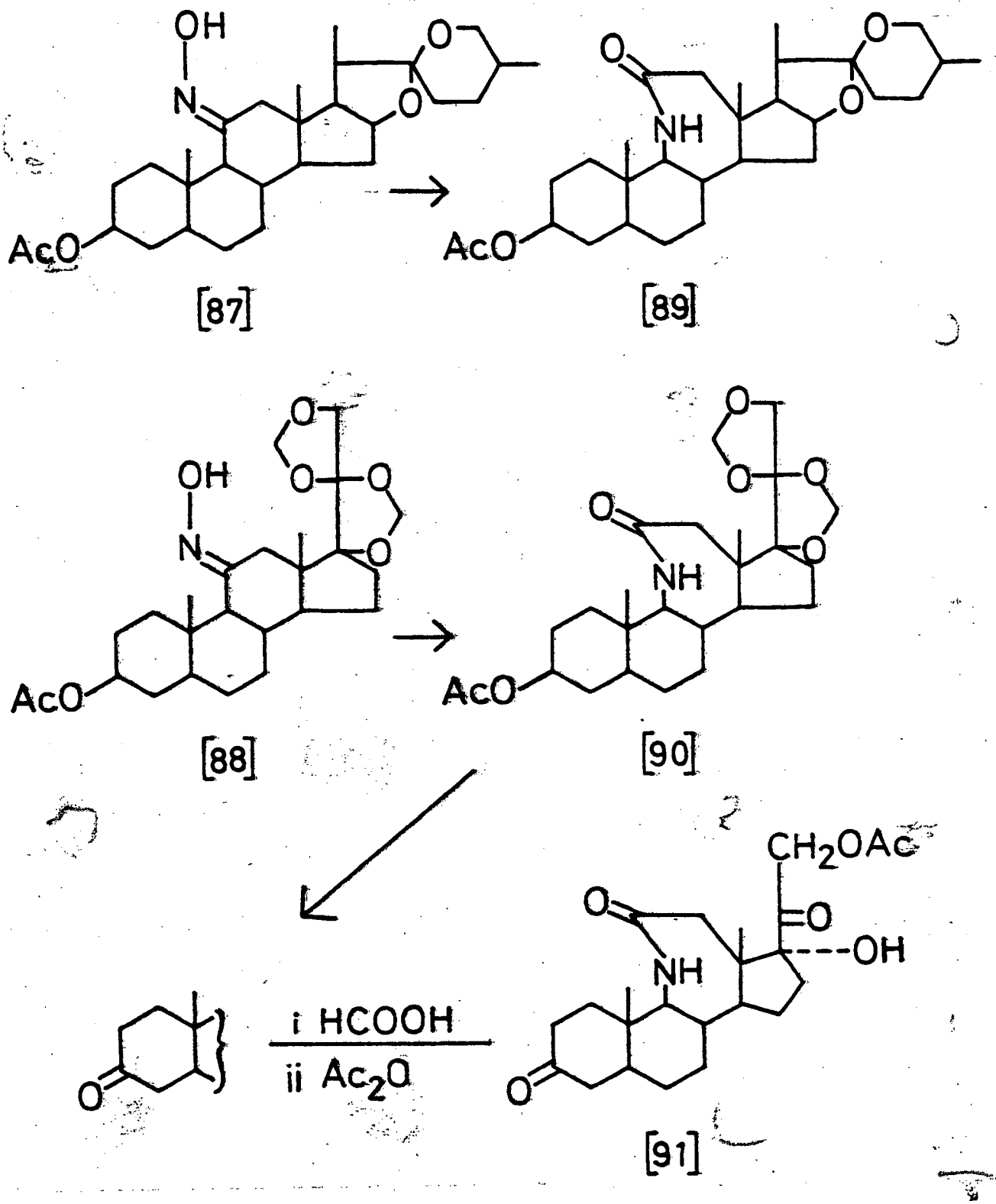
followed by hydrolysis, led to 3β-methoxy-6β-hydroxy-5β,19-cyclo-androstan-17-one (80) which, with sulphuric acid and water as nucleophile, gave 3β-methoxy-7β-hydroxy-B-homoestra-5(10)-en-17-one (78). Scheme 20 . Knox et al.[41] had used the same reaction but used fluorine as nucleophile. They found the yields very much dependent on conditions of temperature, choice of solvent and method of isolation as expected. A 63% yield of 7ξ-fluoro-B-homo derivative (77) was obtained by using methylene chloride as solvent at -20°C with diethyl (2-chloro-1,1,2-trifluoroethyl)amine and passing the gross reaction mixture, after forty-eight hours, through an alumina column. The eluted oils were combined and chromatographed on florisil which gave 3β-acetoxy-7ξ-fluoro-B-homoestra-5(10)-en-17-one (77) as a crystalline solid on elution with hexane:ether.

None of the methods for ring-A and ring-B expansion had been used for ring-C homologation. However, a C-homosteroid had been prepared in 1963[42] from 5β-pregnane-17α,21-diol-3,11,20-trione (81) by a seven stage synthesis. Scheme 21 . The starting material was converted to the 3,3-ethylenedioxy-17α, 20:20,21-bis(methylenedioxy) derivative (82) in two steps to protect the C-3 and C-20 ketones. The 11α-methyl-11β-hydroxy adduct (83) prepared by the action of methyl lithium on the C-12 ketone was treated with thionyl chloride in pyridine as a dehydrating agent leading to 11-methyl-3,3-ethylenedioxy-17α,20:20,21-bis(methylenedioxy)-5β-pregn-9(11)-ene (84). Hydrolysis to remove the ethylene ketal group followed by ozonolysis and treatment with methylene phosphite in the presence of 10% perchloric acid afforded a seco-steroid (85). Ring closure with potassium tertiary butoxide gave the required ring-C expanded product, 17α,20:20,21-bis-(methylenedioxy)-C-homo-5β-pregn-9-ene-3,12-dione (86). Previous to


CH2OH
C=O
OH
O
O
H
[81]
O
O
O
O
D
A
O
O
H
[82]
CH3
HO
O
O
O
O
O
O
H
[83]
H3C
C
[84]
A
O
H
O
O
O
O
O
O
O
H
[85]
O
O
O
O
O
O
H
[86]

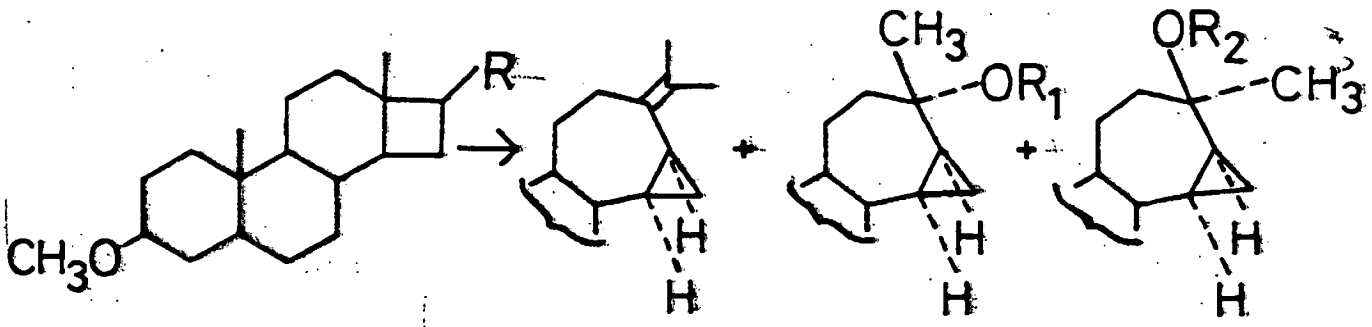
Scheme 21

this, only the 9a-aza-C-homo skeleton has been made. This was accomplished by Zderic and Iriarte[43] in 1962 by a Beckmann rearrangement of the oximes of 3-acetoxy-tigogenin (87) and 3-acetoxy-17α,20:20,21-bis(methylenedioxy)-androstan-11-one (88). Reaction with phosphorous oxychloride in anhydrous pyridine caused the rearrangement affording 9a-aza-C-homotigogenin-11-one-3-acetate (89) and the corresponding homologue of the androstane derivative (90). Further treatment of the 9a-aza-C-homo-androstane with chromic acid to the C-3 ketone followed by removal of the bis (methylenedioxy) group in warm 60% formic acid then acetylation gave 21-acetoxy-17α-hydroxy-9a-aza-C-homopregna-11, 20-dione(91). Scheme 22 .


OH
N
O
O
AcO
[87]
O
NH
O
O
AcO
[89]
OH
N
O
O
O
O
AcO
[88]
O
NH
O
O
O
O
AcO
[90]
CH2OAc
O
O
---OH
NH
O
O
[91]
i HCOOH
ii Ac2O

Scheme 22

In 1970, two series of reactions were carried out by separate groups to form the C-homo-D-nor steroids. Meinwald and Wheeler[44] in fact formed a C-homo-D-bisnor structure by nitrous deamination reactions of pseudoequatorial D-norandrostanyl-16β amine (92), thermal decomposition of the 16β-N-nitroso derivative (93), hydrolysis of the 16β-diazotate salt (95), and solvolysis of toluene sulphonates (102). Scheme 23 . Two conformational isomers with the C-homo-D-bisnor structure (97) and (100) were formed in the nitrous deamination reaction at -10°C in acetic acid followed by lithium aluminium hydride reduction.



R=NH2 [92] [96] R1=H [97] R2=H [100]

R=N(NO)COOCH3 [93] R1=CH2CH3 [98]

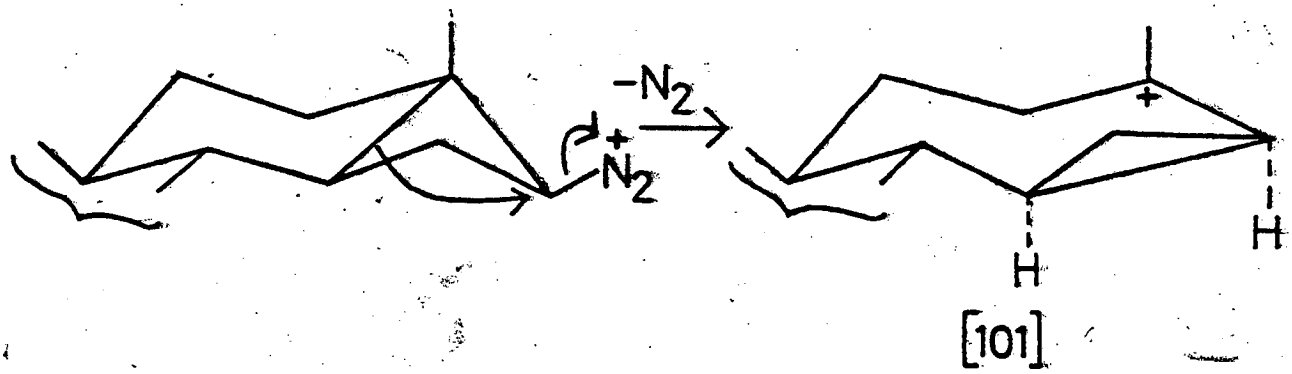
R=N(NO)COCH3 [94] R1=Ac [99]

R=N=N—O⁻⁺K [95]

Scheme 23

The thermal decomposition of the 16β-N-nitroso derivative at 75°C again led to two products. Only one isomer (98) corresponding to the nitrous deamination products, plus a C-homo-D-bisnor adduct containing an exocyclic olefinic double bond (96). Thermal decomposition of the 16β-N-nitrosoacetamide (94) at 45°C in buffered

solution led to the same products (122)(124), except for the acetate group on the C-ring in accord with the nature of the starting material. The diazotate salt (95) of the 16β-N-nitrosocarbamate, on hydrolysis with water, gave the olefinic species (96) and the alcohol (97) as the major product. All the products were shown to arise from the same intermediate carbonium-ion (101) formed by rearrangement of the original carbonium ion from deamination of the various starting materials. The differing conditions led to varying yields of products;Table 5. Scheme 24 .



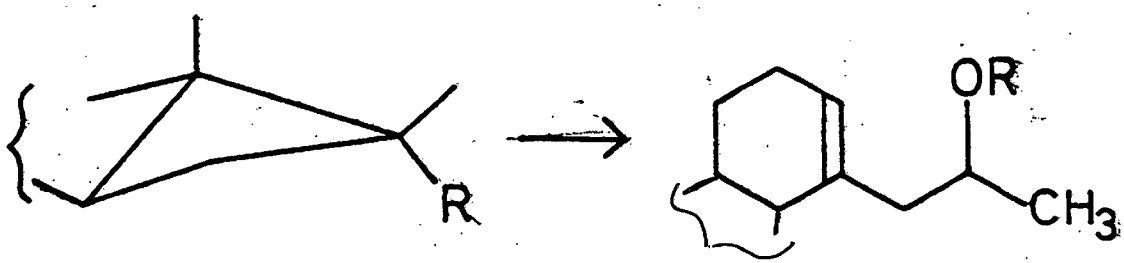
Scheme 24

Starting Material	Products %				
	(96)	(97)	(98)	(99)	(100)
(92)		69			18
(93)	40		32		
(94)	50			42	
(95)	9	88			

Table 5

The solvolysis of 3β-methoxy-D-norandrostanyl-16β-toluene sulphonate in dioxan and water, gave the same isomeric mixture as did the nitrous deamination (97) and (100) in yields of 28% and 48% after three days stirring at room temperature with calcium carbonate. The

16α-toluene sulphonate (102) formed, under similar conditions, an olefinic seco-steroid (103) which was also the product of nitrous deamination of the 16α-amine (104) as the corresponding alcohol (105). Scheme 25 .

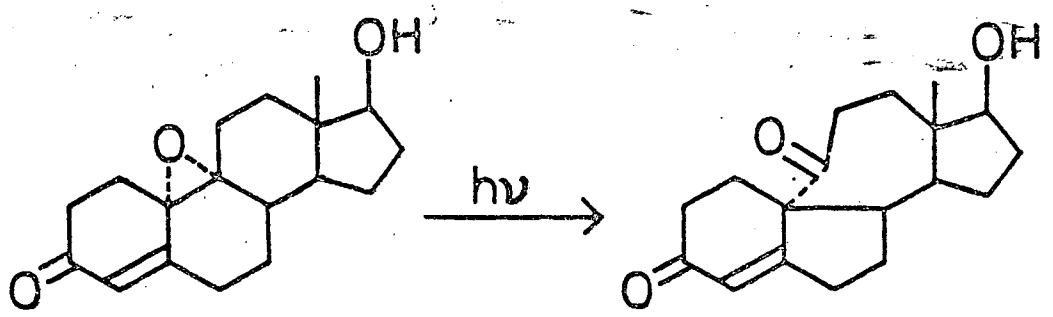


R = OTs [102] R = Ac [103]

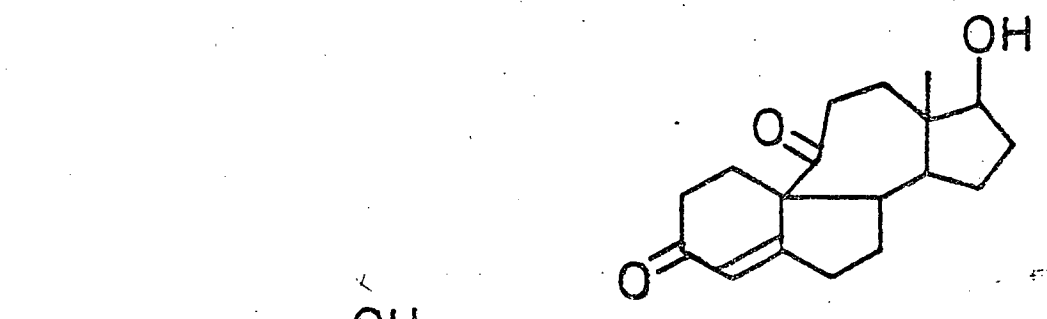
R = NH_2 [104] R = H [105]

Scheme 25

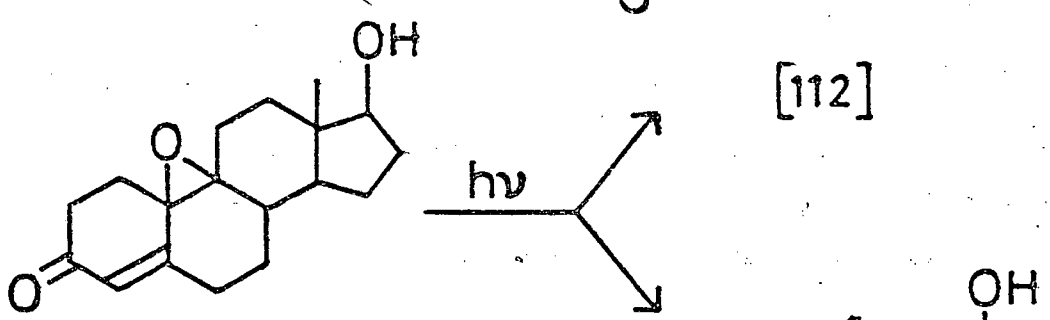
The second set of reactions, carried out by Tamm[45], involved a Pinacol type rearrangement of the 15-mesylate of 3-acetoxy-14α,15α-dihydroxycard-20-enolide (106) by treatment with sodium iodide in refluxing acetic acid to give the product (107) in 20% yield. The corresponding 17β-acetoxy derivative gave no C-homo-D-nor product, only a 15-oxo-Δ^{16}-hydroxy steroid (108). Scheme 26 .



[109] [110]

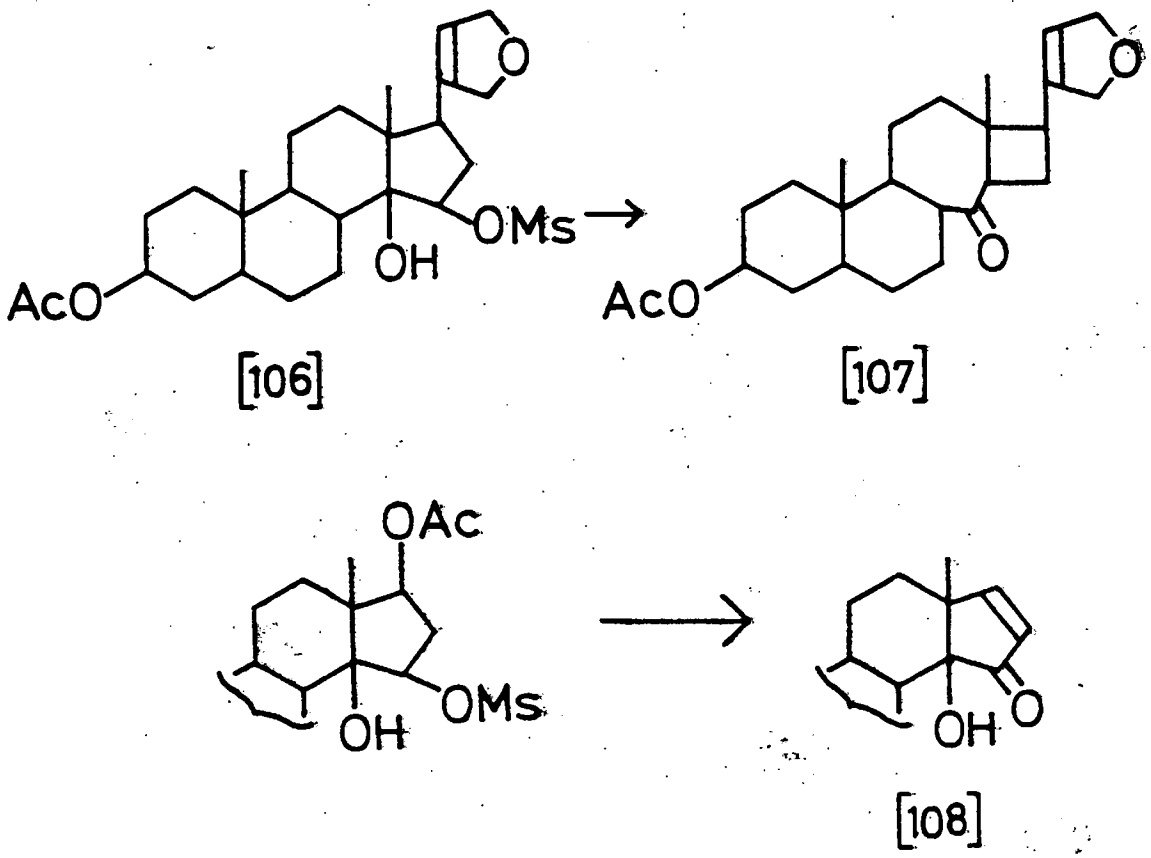


[112]



[111] [113]

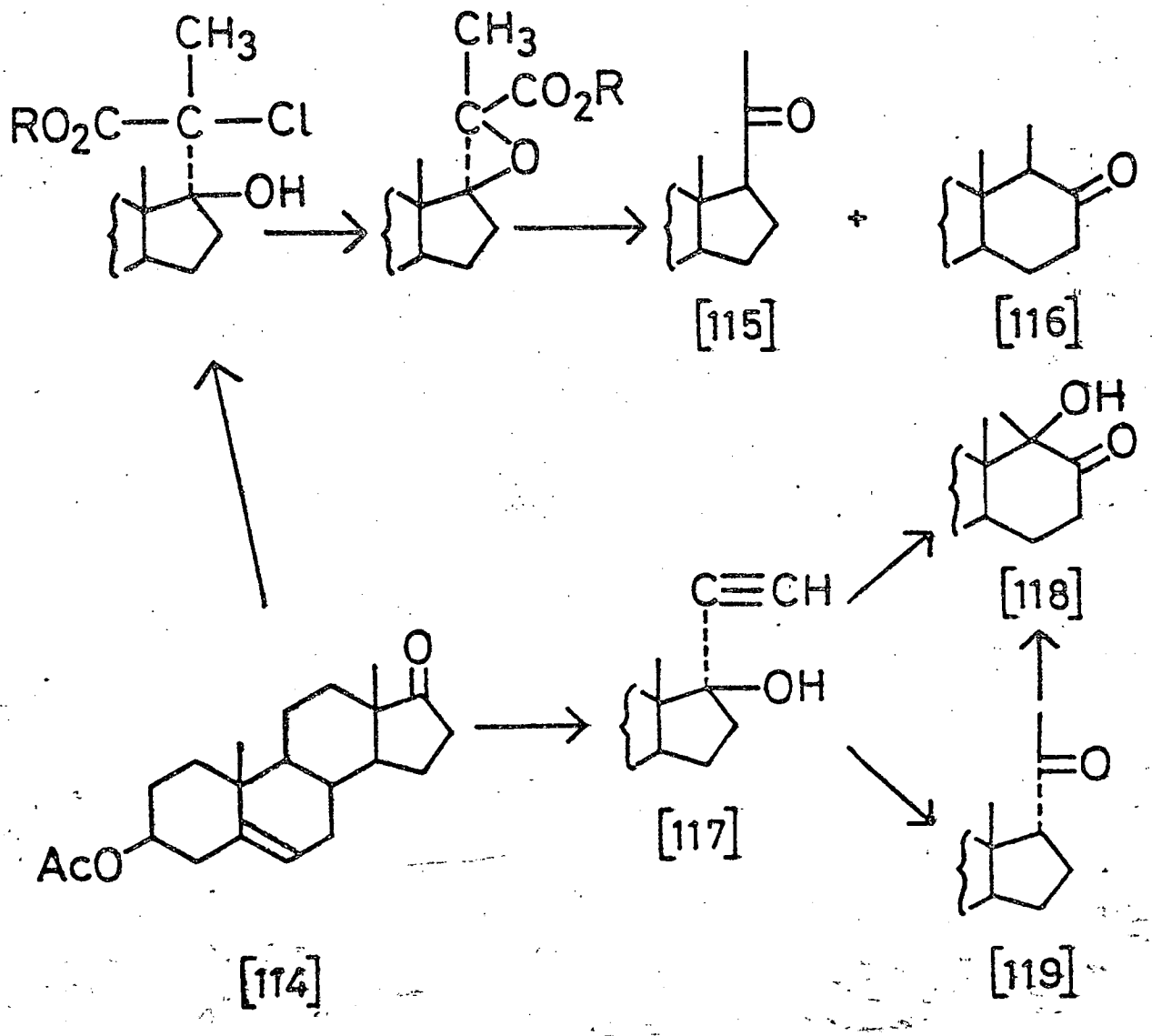
Scheme 27



Scheme 26

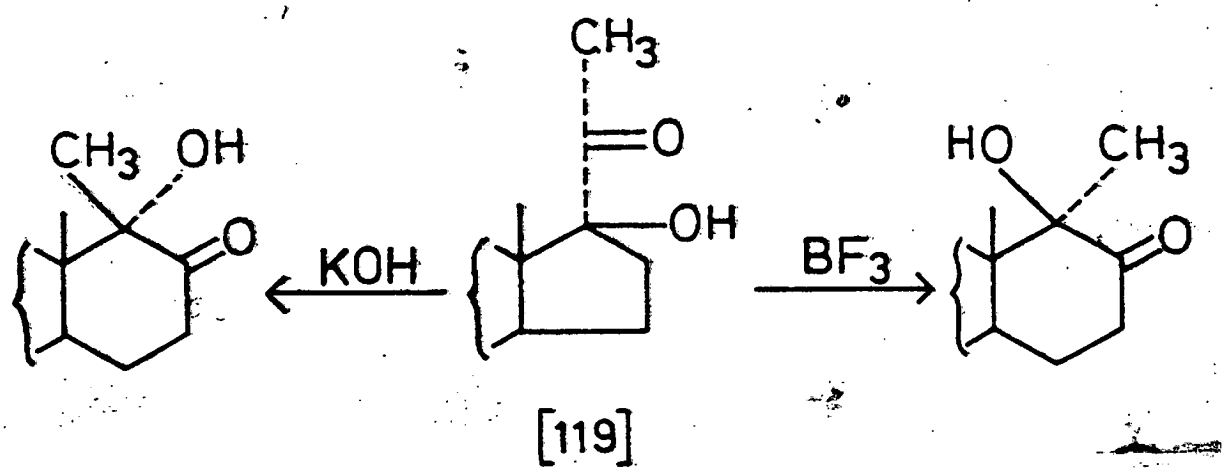
Again in 1970, Debono et al.[46] prepared the C-homo-B-nor skeleton by photolysis reactions. Irradiation of 9α-,10α- and 9β,10β-oxidoestr-4-en-3-ones (109) and (111) with ultra-violet light (2537 Å) in t-butanol brought about the rearrangement giving a C-homo-B-nor-diketone (110) as the exclusive product in 70% yield from 9α,10α-oxido-ketone, and its configurational isomer (112) plus a 10,14-cyclo-diketone (113) in ratio 3:1, from the 9β,10β-oxido-ketone. Scheme 27 .

The homologation of ring-C has been by far the least studied where as ring-D expansion reactions were the first known and extensive work has been done on these reactions and their products. Steroids in which ring-D is enlarged by one carbon atom, were first encountered in attempts to apply two different synthetic methods for introduction of a two carbon side chain corresponding to that of progesterone into the C-17 position of androstenolone. Both the expected pregn-5-enolone (115)


CH3
RO2C—C—Cl
OH
CH3
CO2R
O
O
O
[115]
[116]
OH
O
C≡CH
OH
[118]
O
AcO
[117]
O
[114]
[119]

Scheme 28

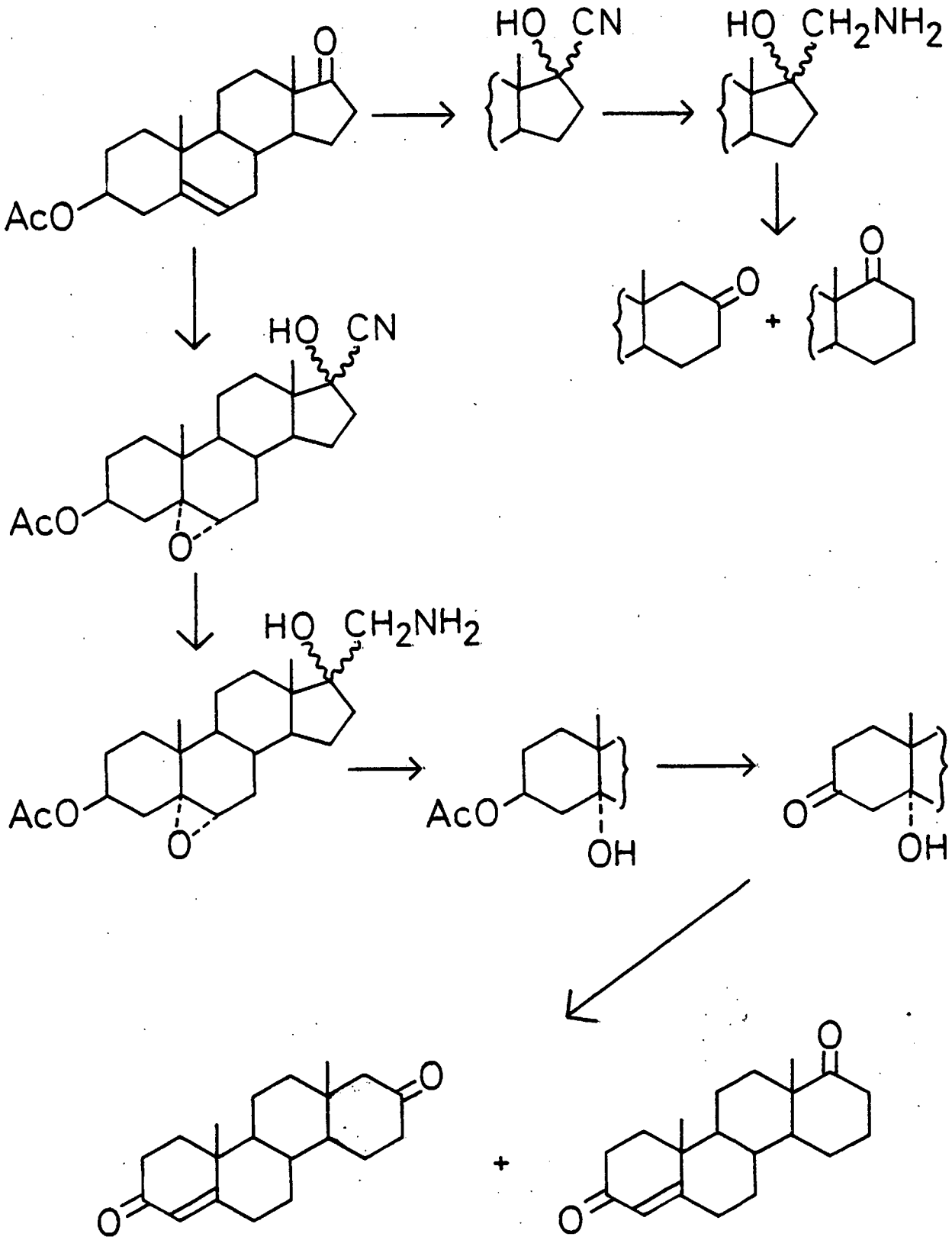
and an isomer shown by Miescher and Kagi[47] to be 17a-methyl-D-homoandrostenol-17-one (116) were formed on Darzens condensation of androstenolone acetate (114) with ethyl α, α-dichloropropionate, followed by alkali treatment and decarboxylation. Scheme 28 . A related product to this anomolous isomer (116) resulted from an attempt to hydrate the 17α-ethyl carbinol of androstenolone acetate (117) to the 17α-acetocarbinol (119). The α-orientation of the ethynyl group was, at the time, unknown and direct hydration in the presence of a mercuric salt, or the addition of acetic acid to the triple bond and hydrolysis, gave a D-homohydroxyketone (118). The normal product (119) was made by Stavely[48] by treatment of the 17α-ethyl carbinol with mercuric chloride-aniline and was found to readily undergo homoannulation to either the α-methyl-β-hydroxy- or β-methyl-α-hydroxy- epimers by adjustment of the conditions. Scheme 29 .



[119]

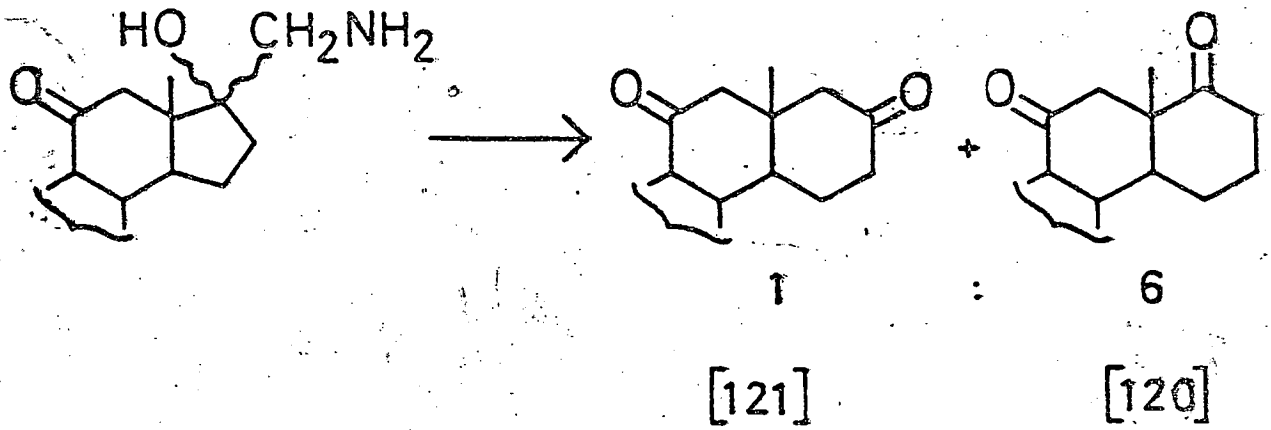
Scheme 29

Tiffeneau-Demjanov ring enlargement was first applied to the D-ring by Goldberg and Monnier[49,51] in 1940 to the 17β-hydroxy-20-amine obtained by hydrogenation of androsterone cyanohydrin. Treatment with nitrous acid gave D-homoandrosterone. D-Homotestosterone[50] was



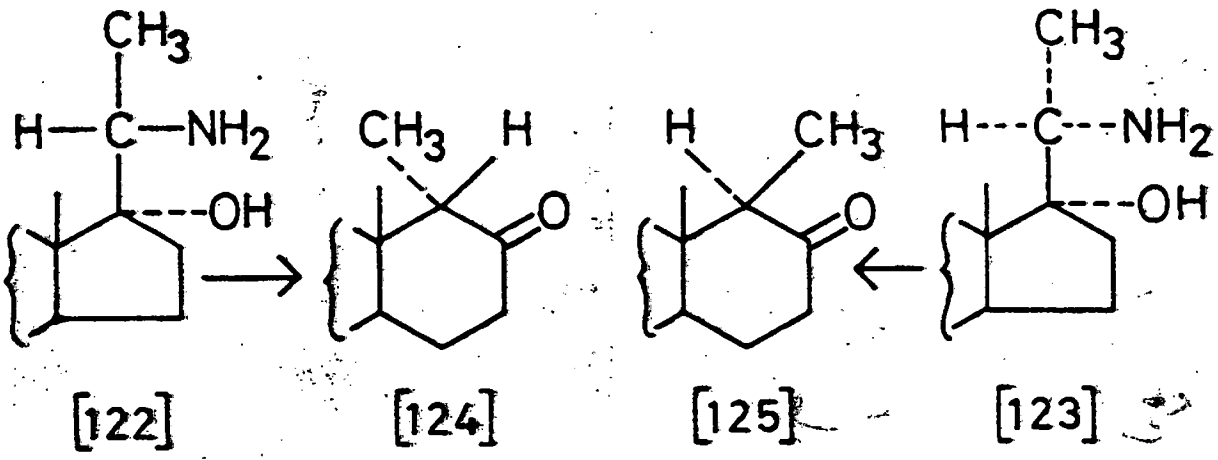
Scheme 30

prepared by protecting the double bond of androstenolone acetate by convertion to the 5,6-oxide. After convertion to the amino alcohol and rearrangement, the oxide ring was reduced to the 5α-ol which was eliminated after oxidation at C-3. Reduction with lithium aluminium hydride proved an easier method for double bond retention. Scheme 30 .



Scheme 31

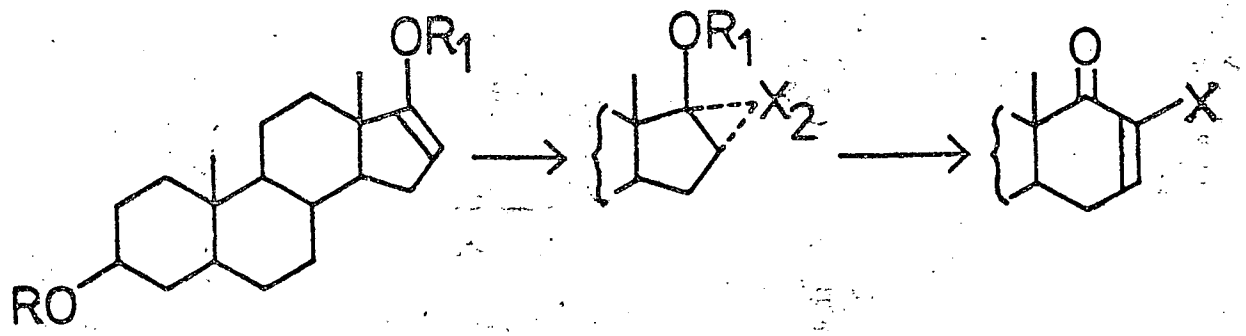
In the preparation of D-homoepiandrosterone, the 17a-ketone was accompanied by a small amount of the isomeric 17-ketone[52]. Wendler et.al.[53] established that the course of the rearrangement is in fact independent of the C-17 configuration, both epimeric amino alcohols of the 3α-acetoxy-11-ketopregnane series affording, on rearrangement, an approximately 6:1 mixture of both 17a- and 17-D-homoketones. (120) and (121). Scheme 31 . The action of nitrous acid on 17α-hydroxy-20-amino-C-21-steroids also leads to D-homoannulation, and Ramirez and Stafiej[53a] found that the 20-epimers (112) and (123) give the epimeric 17α-methyl-D-homo-17-ketone (125) respectively. They interpret the stereospecificity of the reactions in terms of steric strain in a bridge-type transition state. Scheme 32 .



Scheme 32

More recent work by Kirk et al.[54] repeating the Tiffeneau-Demjanov rearrangement, found the D-homo-5α-androstan-17a-one and -17-one from dehydroepiandrosterone in approximate ratio 20:1 respectively.

In 1971, Johns and Salamon[55] used the method of carbene addition to enol ethers and acetates followed by rearrangement of the resulting cyclopropyl derivatives. The dibromo- and dichlorocarbenes were generated from haloform and potassium tertiary butoxide, the addition products (127) and (128) being unable to be isolated but rearranging directly to the conjugated monohalide ring expanded products (129) and (130). 17β-Methoxy-16a, 17-cyclopropano -androstan-3β-ol acetate (132) was prepared by addition of carbene from diethyl zinc and methylene iodide, the rearrangement to the required D-homo product (133) being accomplished with iodine. This reaction was also done on the corresponding enol acetate (134). Scheme 33 .



R= Ac; R_1= Et [126] R=H; R_1=Et; X = Cl [127] R=H; X=Cl [129]

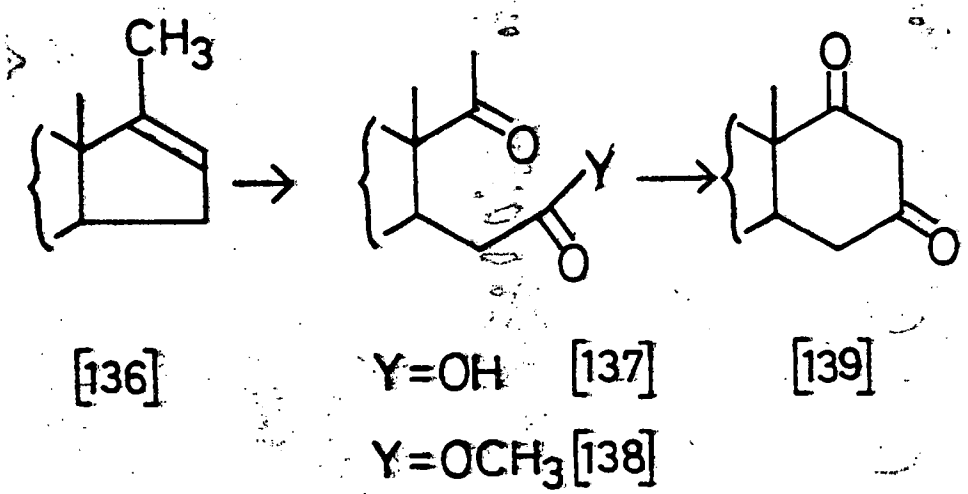
R= Ac; R_1= CH_3 [131] R=H; R_1=Et; X = Br [128] R=H; X=Br [130]

R= Ac R_1= Ac [134] R=Ac; R_1=CH_3; X= H [132] R=Ac; X=H [133]

R=Ac; R_1=Ac ; X= H [135]

Scheme 33

The dichlorocarbene was also made from the thermal decomposition of sodium trichloroacetate to form the same homologated steroid. An alternative ring expansion shown in this work, was via a seco steroid (138) formed by the action of sodium metaperiodate and ruthenium dioxide on the 17-methyl-Δ^{16}-steroid (136) giving 3β-hydroxy-17-keto-17-methyl-16,17-seco-androstan-16-oic acid methyl ester after treatment. of the acid(137) with diazomethane. Reaction with sodium methoxide formed the ring-D expanded diketone (139). Scheme 34 .



[136] Y=OH [137] [139]

Y=OCH3 [138]

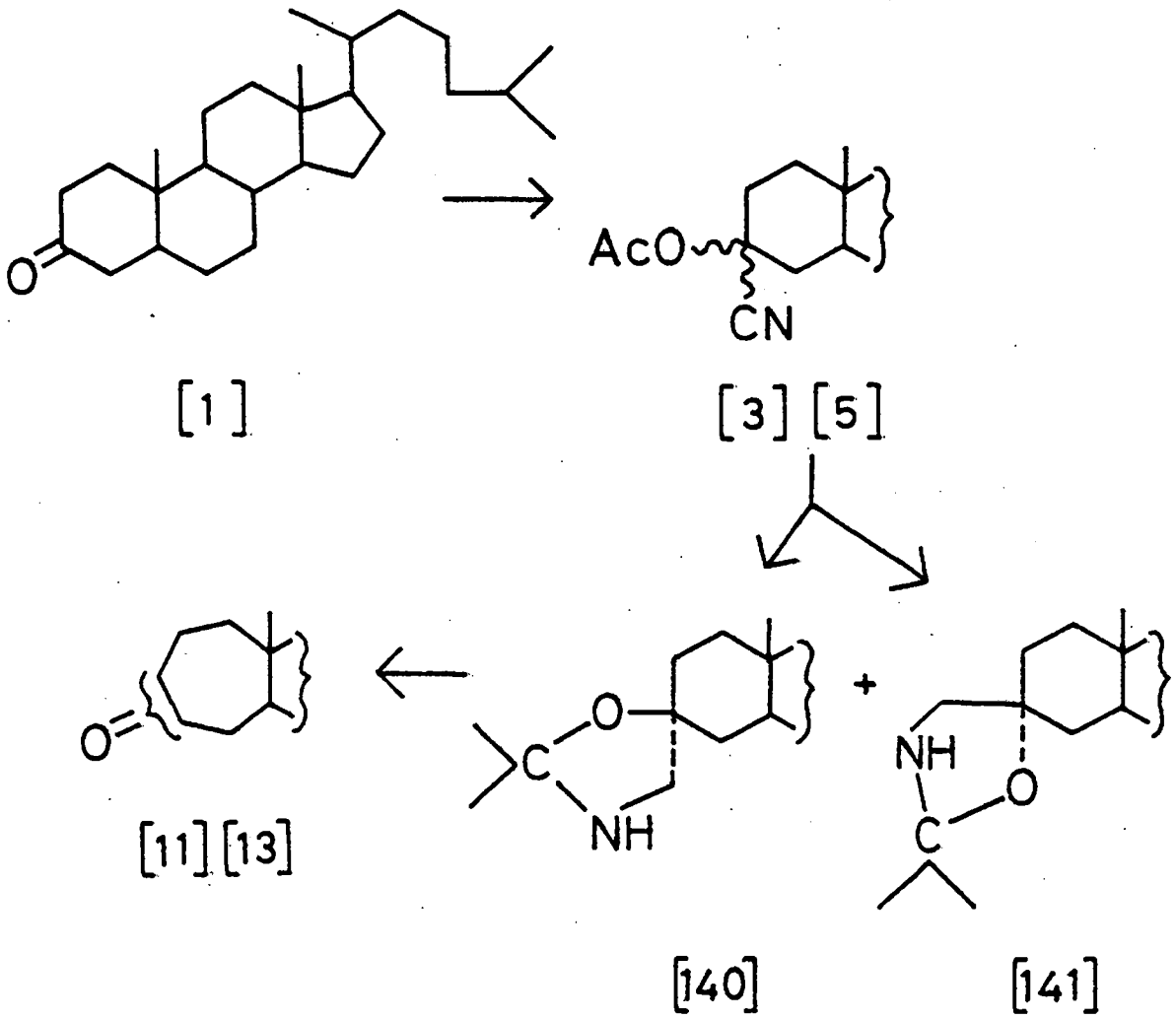
Scheme 34

Ring-D expansions have been known for many years so there are many more homologation rearrangement reactions, only the best known types have been summarised. Further syntheses of ring expanded steroids were commenced, the enlargement of the C-ring being studied more closely because of the existence of only limited data on homologation of this ring. The results of the investigations are described in the following sections.

2. Discussion

2.1 Tiffeneau-Demjanov Rearrangements

The reaction route leading to Tiffeneau-Demjanov rearrangements was used by Goldberg and Kirchensteiner[4] to obtain the first known homosteroids by the homologation of cholestan-3-one and androstan-3-one. Scheme 35 . Repetition of the scheme as a template for further studies was undertaken, not only by the original method but also by a slightly modified version in as much as the cyanohydrins were prepared by reaction of chelestan-3-one (1) with acetone cyanohydrin in the presence of base at room temperature, as well as by reaction with potassium cyanide, the former giving better yields under milder and less hazardous conditions. Acetylation and one recrystallisation of the resulting product from methanol afforded the expected pair of cyanohydrin acetates (3) and (5). Further recrystallisations gave pure 3β-acetoxy-3α-cyano-cholestane (3) but the mixture was used in the hydrogenation and subsequent rearrangement, the stereochemistry having already been shown to have no effect on the ratio of homologues produced[15]. Reduction with lithium aluminium hydride to the hydroxy-amines (7) and (9) followed by slow distillation of their acetone solution formed the corresponding acetonides (140) and (141) which crystallised from the cooled residue as a white solid. The n.m.r. spectrum of the mixed acetonides showed peaks at τ6.94 and τ8.65 which have been assigned to the two protons α to the imino group and to the geminal methyl groups respectively. Nitrous deamination of these acetonides and chromatography of the product on alumina gave, on elution with petrol-ether, a ring-A expanded steroid ketone, shown by Levisalles et.al.[15] by optical rotary dispersion and circular dichroism techniques to be a mixture of A-homocholestan-4-one (13)



Scheme 35

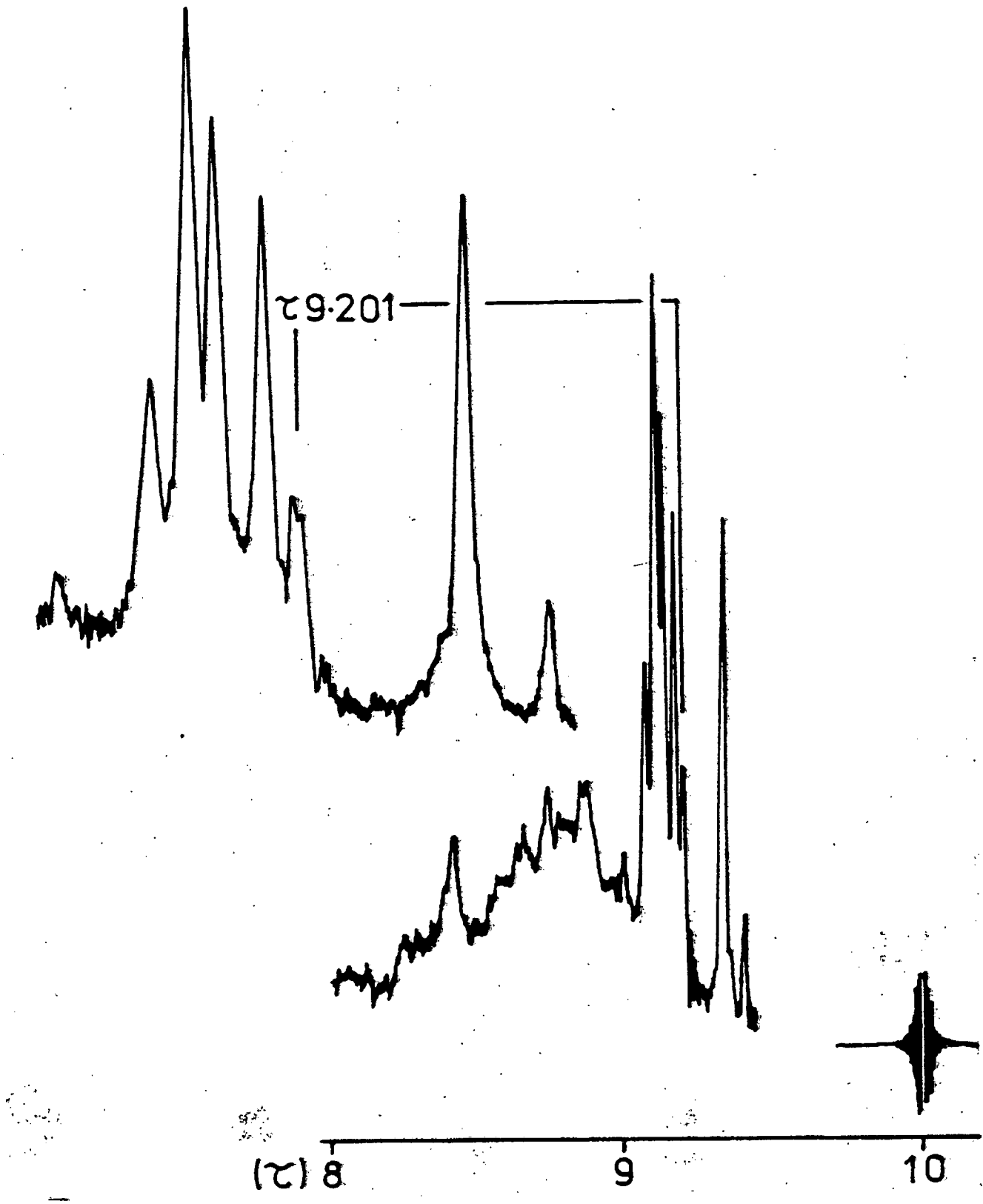


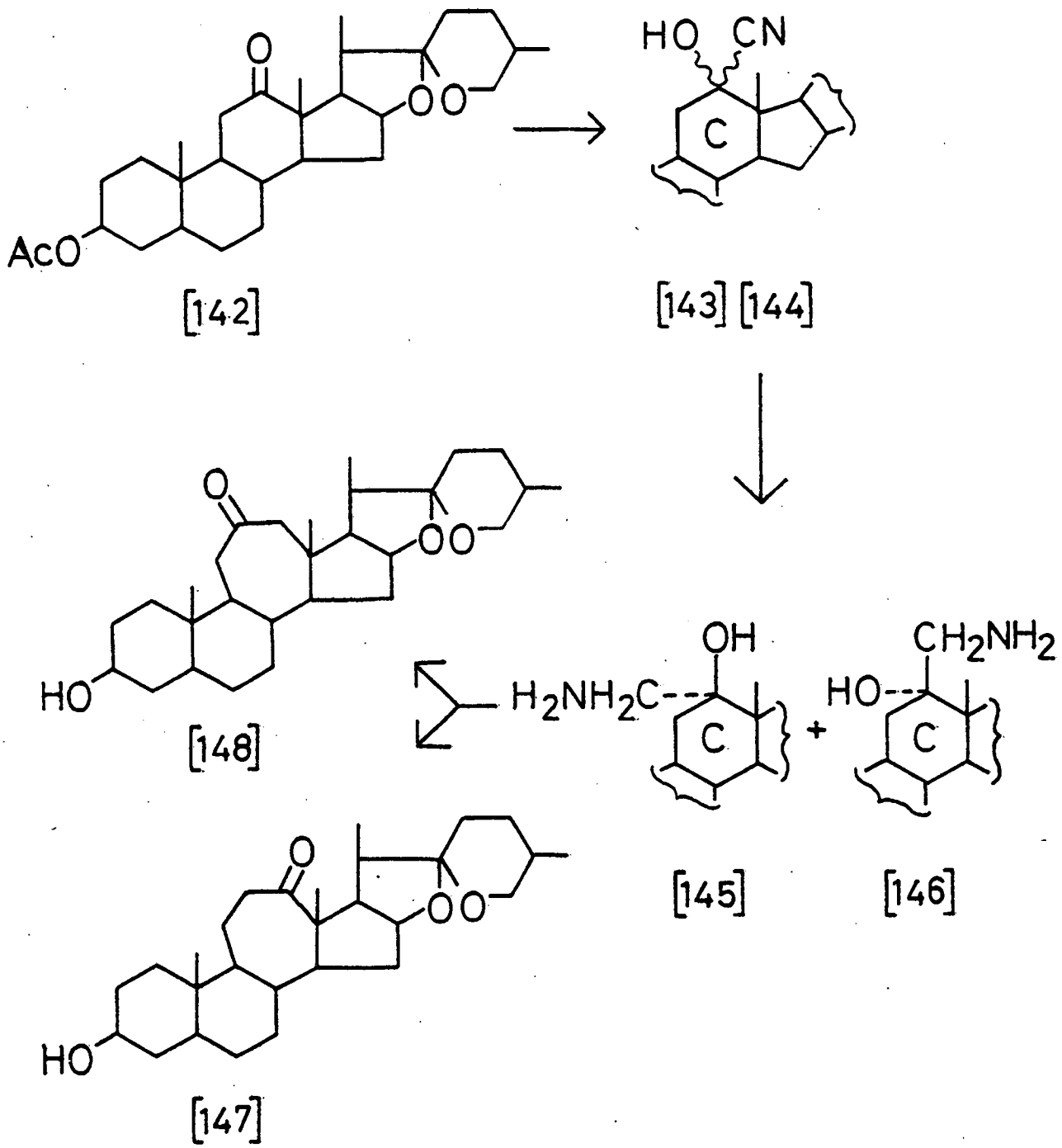
fig. 1. n.m.r. spectrum of A-Homocholestan-3-one and 4-one mixture with expansion showing the split peak at τ 9.201

and A-homocholestan-3-one (11) which, although indistinguishable by chromatography, infra-red or mass spectra, do show a slight difference in chemical shift of the C-19 methyl signals in the n.m.r. spectrum. Expansion of the spectrum of the ketonic mixture shows the broadened peak at τ9.201 in the original spectrum split into two peaks of equal intensity substantiating the presence of an appriximately 50:50 mixture of homologous ketones as put forward by Levisalles Fig 1 . The A-homocholestanones were produced in 10% overall yield from cholesterol, the results compared with previous work are summarised in Table 6. Scheme 35 .

Compounds	% age yields				n.m.r. (τ)	
	References	9	5	4	C-18 methyl	C-19 methyl
Cholestan-3-one					9.35	9.00
Cyanohydrins	73	89				
Aminomethyl alcohols	61	85		88		
Acetonides	62	81	68		9.38	9.22
A-Homocholestanones	69	70	28	69	9.346	9.201

Table 6

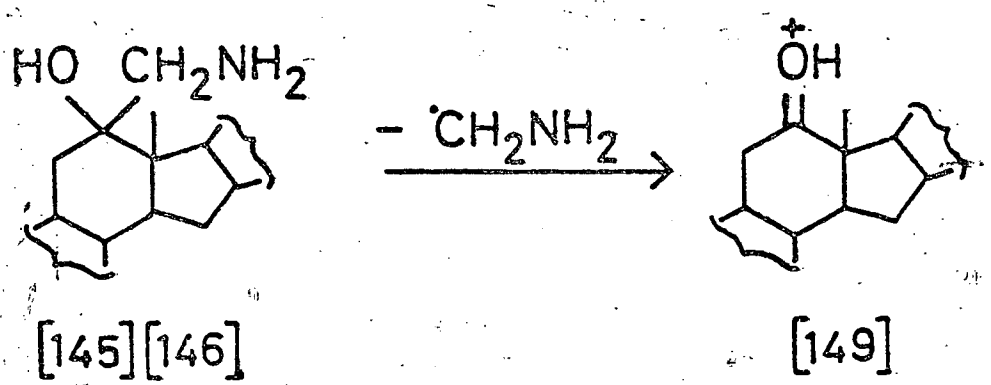
Extension of the scheme to ring-C was attempted with two C-12 ketones as substrates, hecogenin acetate (142) and a derived product of hecogenin, 3β,20β-dihydroxy-pregnan-12-one (152). Hecogenin, a sapogenin which Marker et al.[56] isolated in 1943 and characterised as a 3β-ol of the 5α- series, is extracted from sisal plants from Yucatan and East Africa as a starting material for cortisone production by transportation of the ketone from C-12 to C-11[57], provides a ready source of 12-keto steroid.


AcO
HO
CN
C
[142]
[143] [144]
HO
[148]
H_2NH_2C
OH
CH_2NH_2
HO
C
C
[145]
[146]
HO
[147]

Scheme 36

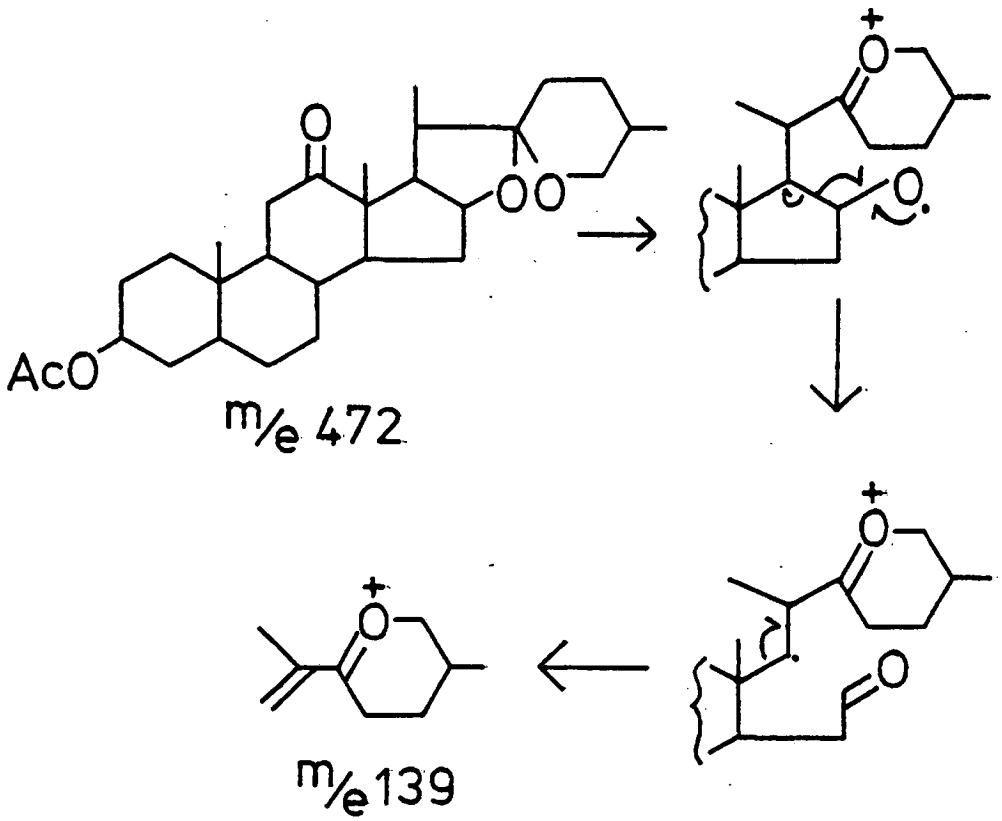
The cyanohydrins of hecogenin acetate (143) and (144) previously reported by Hirschmann et al.[58] and made by reaction of hecogenin acetate with potassium cyanide or alternatively hydrogen cyanide, were prepared in almost quantitative yield by warming a slurry of hecogenin acetate in ethanol until complete dissolution took place. Dropwise addition of triethylamine then precipitated the cyanohydrins which were filtered off. Scheme 36 .

Although Hirschmann assigned the configuration, this seemed unnecessary in the present case as the epimeric hydrogenated cyanohydrins (145) and (146) are assumed to rearrange in a similar manner with nitrous acid as is the case for ring-A and ring-D. Acetylation gave no reaction with the 12-hydroxyl so the cyanohydrins were hydrogenated directly under an atmospheric pressure of hydrogen in the presence of Adams catalyst to give the epimeric 12-aminomethyl-12-hydroxy-tigogenin acetates the mass spectrum of which shows a low intensity molecular ion at $^{m}/_{e}$ 503 (1.5%) and a peak assigned to loss of the aminomethyl group at $^{m}/_{e}$ 473 (15%) (149). Scheme 37 .



[145][146] [149]

Scheme 37



Scheme 38

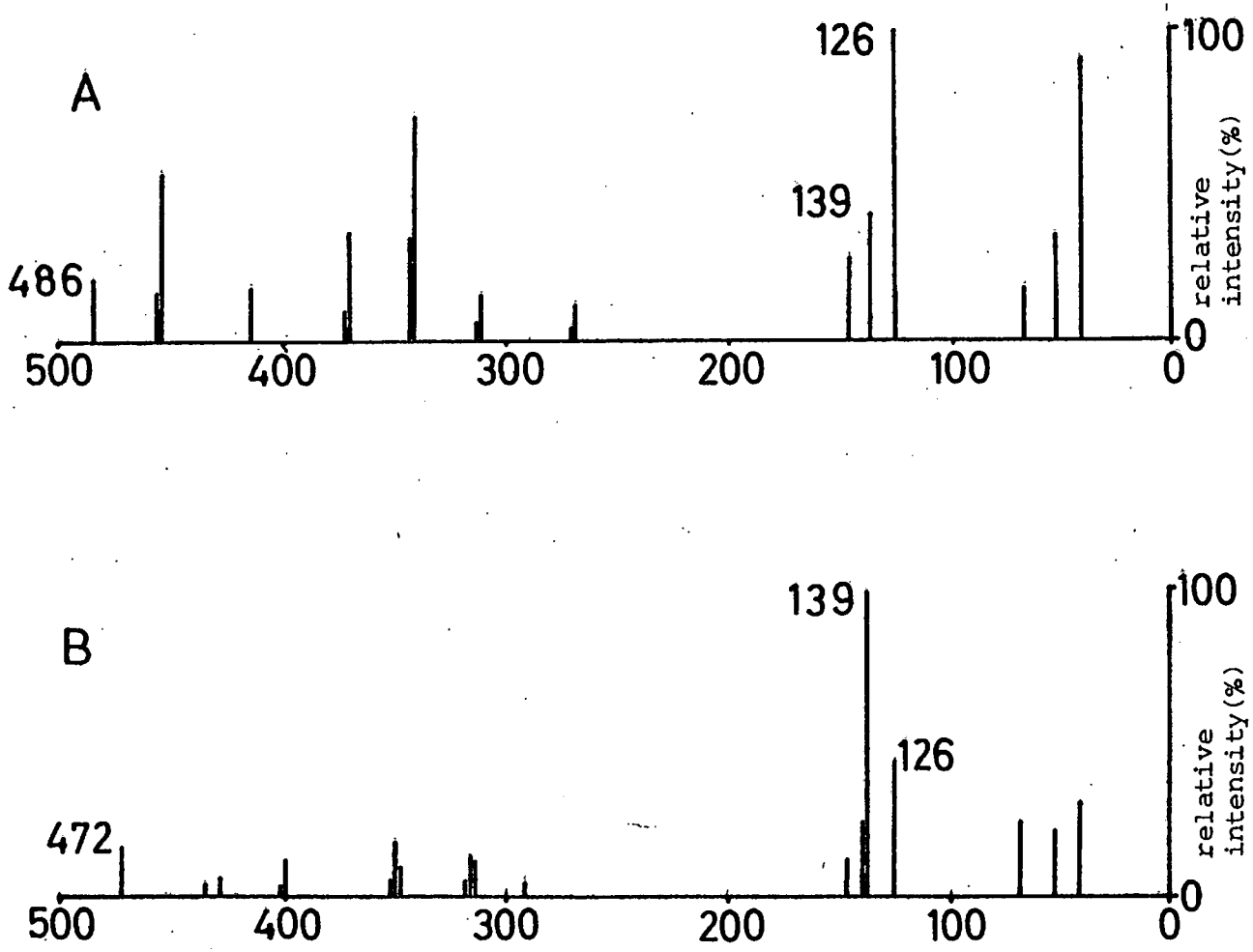
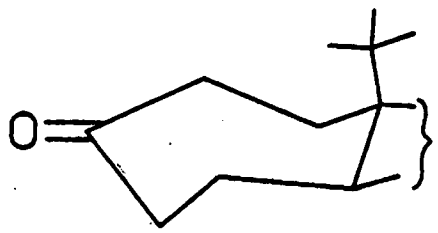


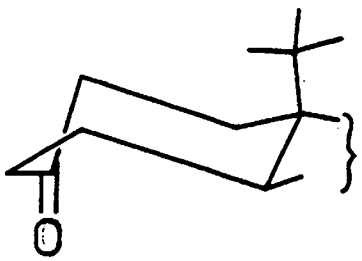
fig.2 Mass specta of C-homohecogenin acetate (148)A and hecogenin acetate (142)B

Nitrous acid deamination gave the crude final product as a gum showing a carbonyl stretch in the infra-red spectrum at 1697cm^{-1}. The mass spectrum shows the molecular ion at $^{m}/_{e}$ 486 (11%) the molecular ion of C-homo hecogenin acetate (147 or 148). The parent ion of hecogenin acetate is $^{m}/_{e}$ 139 arising from degradation of rings-E and -F[59]. Scheme 38 , however, the parent ion becomes $^{m}/_{e}$ 126 in the ring-C expanded homologue. Although the influence of β-carbonyls are well known in determining the fragmentation patterns of steroids in the mass spectrometer, the effect of removal of the carbonyl in hecogenin to a γ-position in respect to C-17 in 12-keto-C-homo hecogenin, (148), one of the possible products in the homologation, can not be invoked in this case to explain the change in parent ion since both Δ^5-11-keto tigogenin (165) and 12-aminomethyl-12-hydroxy-tigogenin (145)(146) have $^{m}/_{e}$ 139 as their parent ion, with less intense peak at $^{m}/_{e}$ 126 (38%). Fig.2.

The twist chair conformations Scheme 39 will be the most stable for the C-homo compounds, the twist chair in the seven-membered rings being 9.24kJ/mole lower in strain energy than the full chair and 10.5KJ/mole lower than the twist boat. Other conformations such as full boat are considered to be energetically prohibitive[60]. As with the six-membered ring 11- and 12-ketones, where an upfield shift of the C-18 methyl signal, and a downfield shift of the C-19 methyl signal in the n.m.r. spectrum on going from the 12- to the 11-ketone are predicted, due to the change in shielding by the carbonyl, so it can be predicted from the conformational isomers, that the two possible products of ring-C homologation, namely C-homo-12-keto-tigogenin acetate (148) and C-homo-12a-keto-tigogenin acetate (147), would give differences in their n.m.r. spectra. The two extreme conformations 39a and 39b of the 12-ketone show similarities to the TC3 and TC4 conformations in the expanded ring-A of A-Homosteroids,[61,62,63] the conformer 39a probably playing the major role due to interaction of the C-18 methyl protons[73]

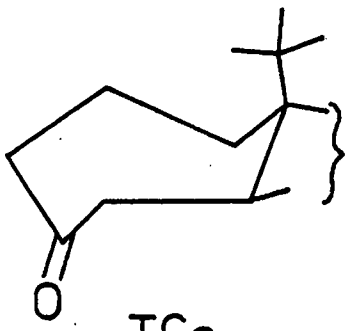


TC3

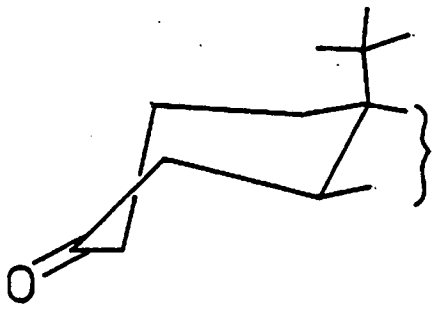


TC4

Extreme conformers of A-homo-3-ketone

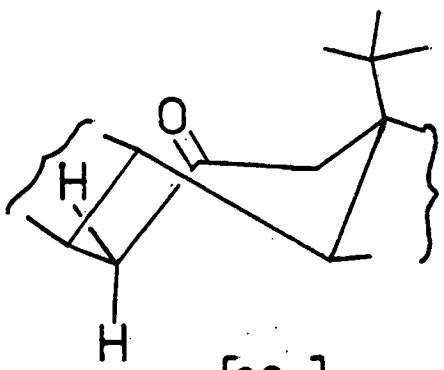


TC3

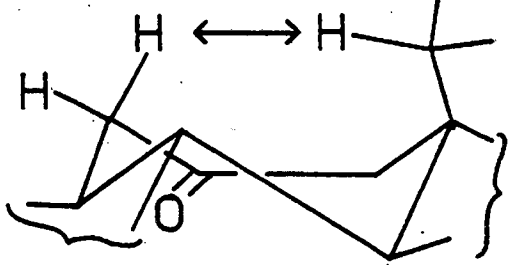


TC4

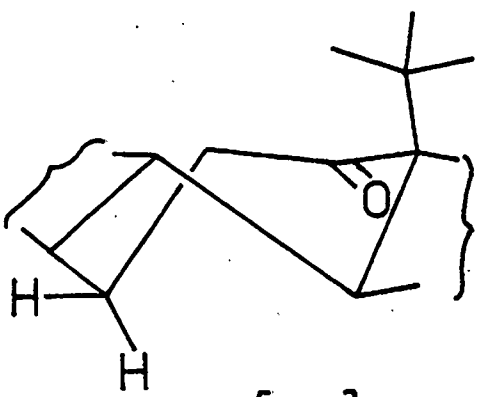
Extreme conformers of A-homo-4-ketone



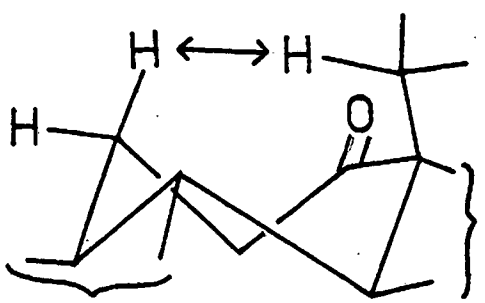
[39a]



[39b]



[39c]



[39d]

Scheme 39

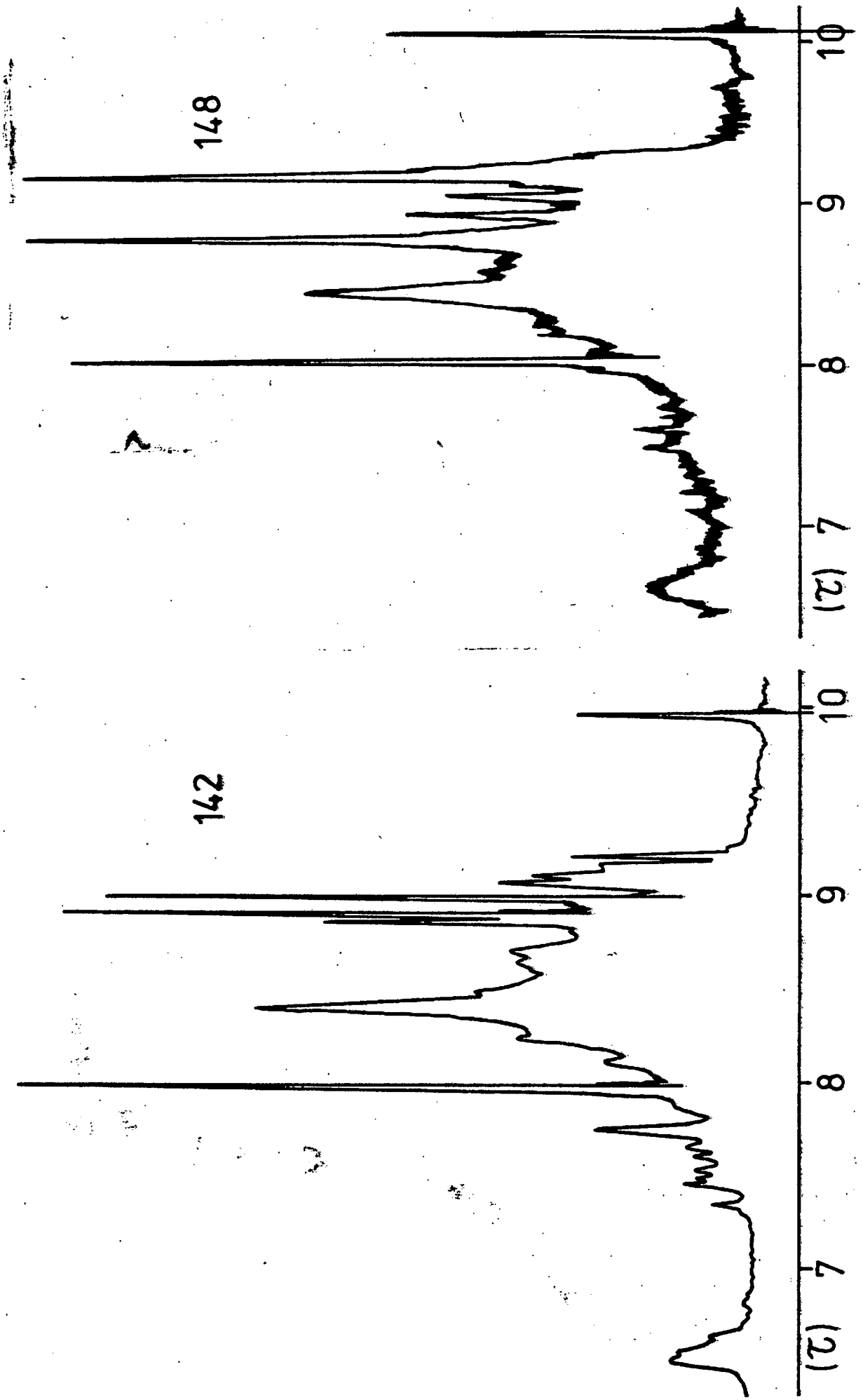


fig. 3 n.m.r.spectra of hecogenin acetate (142) and C-homo-hecogenin acetate (148).

and the β-proton of C-11. This is even more so for the extreme conformers of the 12a-ketone where 39c would play the major role. So a larger upfield shift could be predicted for the C-18 methyl signal in the 12-ketone compared to the 12a-ketone due to a larger degree of steric environmental change of the methyl in relation to the carbonyl in the 12-ketone compared to hecogenin acetate. The n.m.r. spectrum of the product in fact shows only one signal for a C-18 methyl, upfield compared to that for hecogenin acetate and one signal for a C-19 methyl, downfield compared to hecogenin acetate. Table 7 . Fig.3.

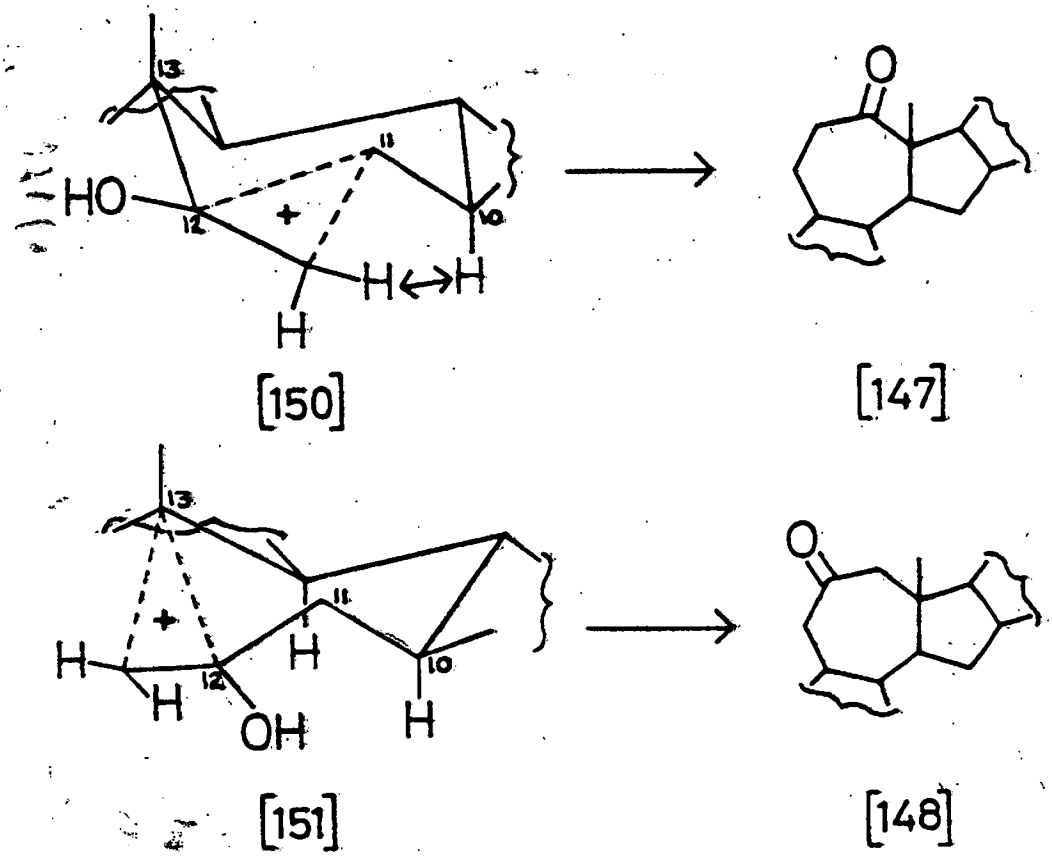
Compound	Methyl signals (τ)	
	C_{18}	C_{19}
Hecogenin Acetate (142)	9.05	8.95
11-keto tigogenin	9.26	8.76
C-homo product (147,148)	9.13	8.74

Table 7

This suggests that in fact C-homo-12-keto-tigogenin (148) is the major if not sole homologated product of the Tiffeneau-Demjanov rearrangement, and that the diminished peak at $^{m}/_{e}$ 139 in the mass spectrum is due to a combination of movement of the carbonyl from a β- to a γ- position with respect to C-17 and change in conformation of ring-C imposed by addition of the extra carbon.

This preference for one isomer is also in line with predictions from study of the Dreiding models of the intermediates in

the rearrangement Scheme 40 , shown here for axial aminomethyl and equatorial hydroxyl, the major constituent (145).



Scheme 40

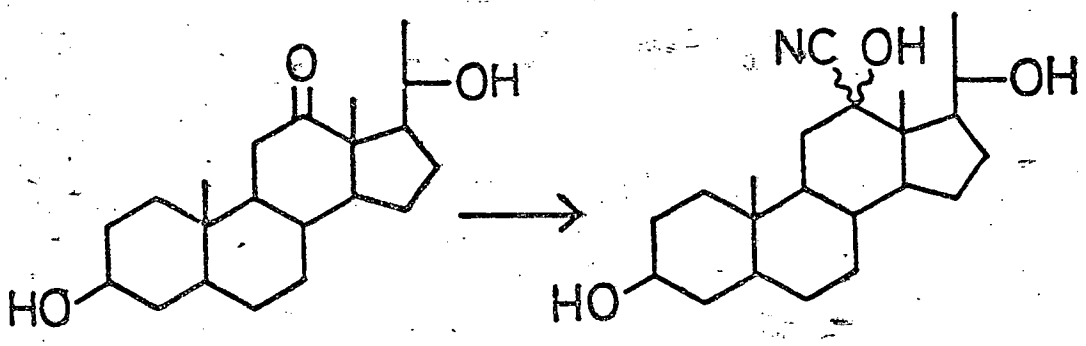
The arguments put forward to explain the erroneous result that the 4-keto homologue was the sole product in Tiffeneau-Demjanov expansion of ring-A, namely that of non-bonded interactions in the intermediates, cannot explain the results of ring-C expansion since the interactions, represented by double-headed arrows, between the C-10 hydrogen and C-12 hydrogen in intermediate (150) leading to the 12a-ketone (147) are shown equally in the intermediate (151) leading to the 12-ketone (148) between the C-12a hydrogen and the C-14 hydrogen Scheme 40. However,

the intermediate three-membered ring leading to the 12-ketone in (151) shows a partial tertiary carbonium ion nature not shown in the intermediate (150), the C-18 methyl will help to stabilise the positive charge and so lead to a preference for this intermediate and hence also for the C-homo-12-ketone (148).

Deuterium exchange gave no definate answer to whether or not only one homologated product is formed since, although a peak appears in the mass spectrum at $^{m}/_{e}$ 448, four mass units above the molecular ion for C-homo-12-keto-tigogenin, peaks also appear at $^{m}/_{e}$ 447 and $^{m}/_{e}$ 446, which, if only the 12-ketone is present, can be explained only by incomplete deuteration.

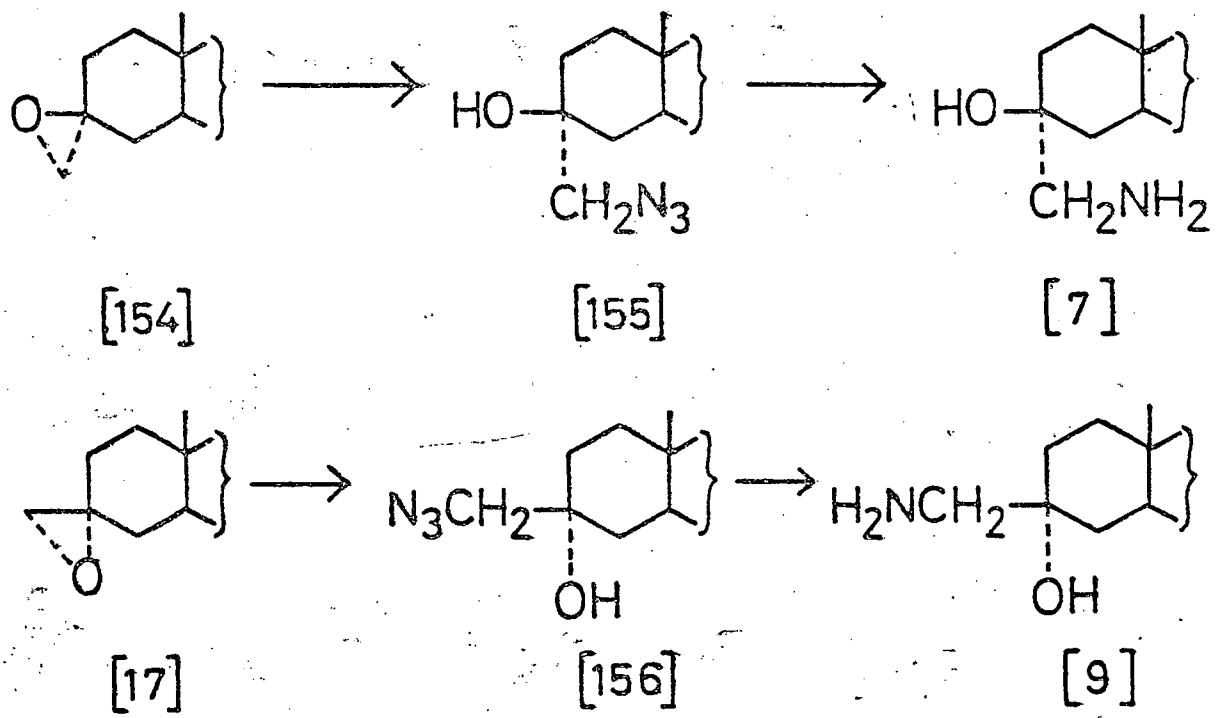
Thin layer chromatography of the product showed only one spot, however, the coincidence of both ring-A homogues suggests that both ring-C homogues would probably also have the same R_f value. Gas chromatography proved impossible for these sapogenins, the samples being adsorbed on the column.

The complete homologation reaction sequence was also applied to 3β, 20β-dihydroxy-pregnan-12-one (152) which gave good yields of cyanohydrins (153) by reaction with potassium cyanide. Hydrogenation under varicus conditions however gave no appreciable amounts of any steroid other than starting material. Scheme 41 .



[152] Scheme 41 [153]

Jones and Price[6] prepared the corresponding ring-A aminomethyl-alcohols (7) and (9) via the exocyclic epoxides of cholestan-3-one (154) and (17) which were converted after the manner of Favre[63] into the hydroxy-azides, 3β-azidomethyl-5α-cholestan-3α-ol (155) and 3α-azidomethyl-5α-cholestan-3β-ol (156), and thence by reduction with lithium aluminium hydride to the aminomethyl-alcohols. Scheme 42.

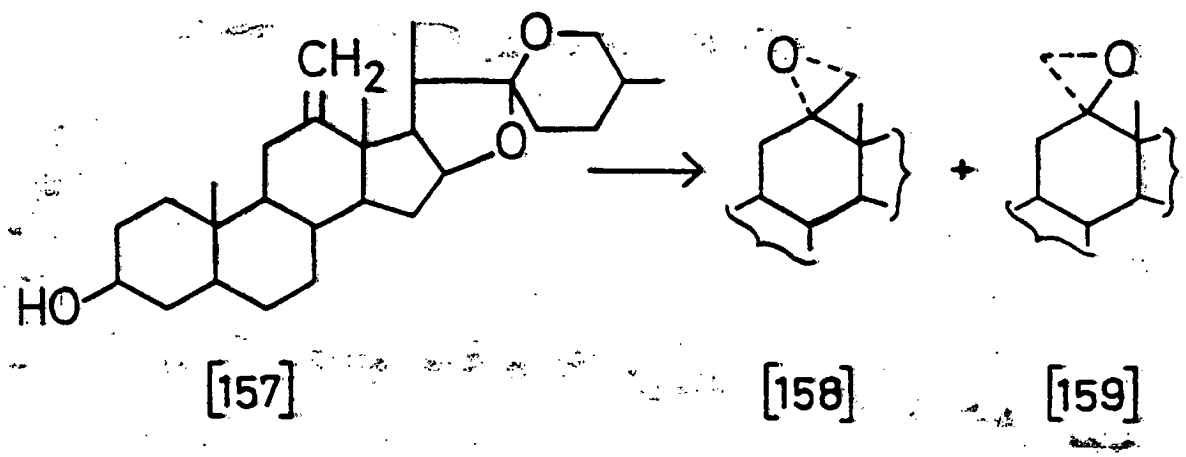


Scheme 42

This offered an alternative route to homo-steroids which was less hazardous, and which gave high yields for the ring-A series.

The exocyclic epoxides at the C-12 position were already known, prepared by Bladon and McMeekin[64] by peracid reaction with

with 12-methylene-tigogenin (157), Scheme 43. Ketones in ring-D had been found to react with trimethyl sulphoxonium iodide [65] and sodium hydride giving exocyclic epoxides[66,67]. Application of this reaction to hecogenin acetate produced an almost quantitative yield of epoxide derivative.



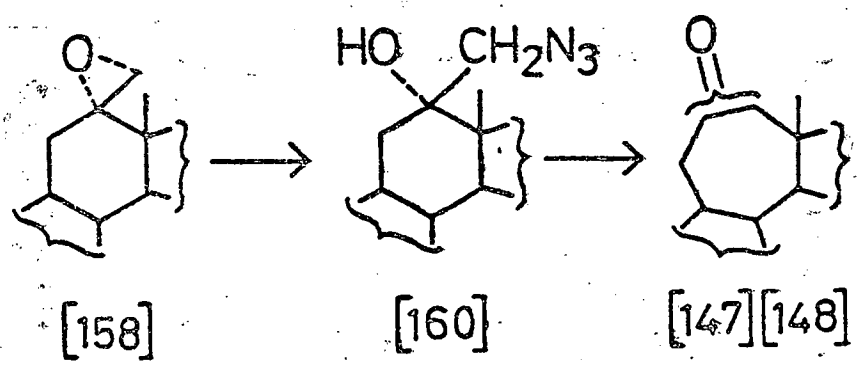
[157] [158] [159]

Scheme 43

The n.m.r. spectrum of the recrystallised product showed, by comparison with previous results, that only the 12,12'-epoxide (158) was present showing a C-18 methyl peak at τ9.16, C-19 methyl peak at τ9.06, and the methylene of the expoxide at τ7.45. There was none of the 12β,12'-epoxide which (159) would have shown peaks at τ9.15 (C-18 methyl), τ9.03 (C-19 methyl), and τ7.03 (epoxide methylene) which however could not be traced.

This preponderence of axial methylene is in line with results of the epoxidation of 12-methylene tigogenin which furnished the 12α,12'- and 12β,12'-epoxides in 2:1 ratio; and with the action of methyl magnesium bromide with hecogenin, which, contrary to earlier reports[68], forms the 12α-hydroxy-12β-methyl derivative as the major product[69,70].

12β-Azidomethyl-12α-hydroxy tigogenin (160) was then prepared in high yield by reacting the exocyclic epoxide (158) with boric acid and sodium azide in refluxing dimethyl formamide. One signal in the n.m.r. spectrum at τ9.20 was assigned to both C-18 and C-19 methyls, the methylene from the 12β-azidomethyl appeared at τ6.68, the expected AB splitting pattern being masked by other peaks due to the sapogenin nucleus. Treatment of the azide with zinc powder and hydrochloric acid causes nitrogen loss. After removal of the zinc nitrous acid was added to perform the rearrangement to the C-homo-steroids. Scheme 44. T.L.C. of the reaction product showed a number of components with two main spots and at least two others. One main spot corresponded to hecogenin whose presence was also indicated in the infra-red (1710 cm^{-1}; 12-ketone) and mass spectra ($^{m}/_{e}$ 430, molecular ion of hecogenin). However, a new carbonyl peak appeared at 1697 cm^{-1} in the infra-red spectrum of this mixture and the mass spectrum gave a peak at $^{m}/_{e}$ 444 (15%) assigned to the molecular ion of C-homohecogenin. This would also correspond to the molecular ion of the exocyclic epoxide of hecogenin, however no evidence for this could be seen either in the infra-red or n.m.r. spectra.



[158] [160] [147][148]

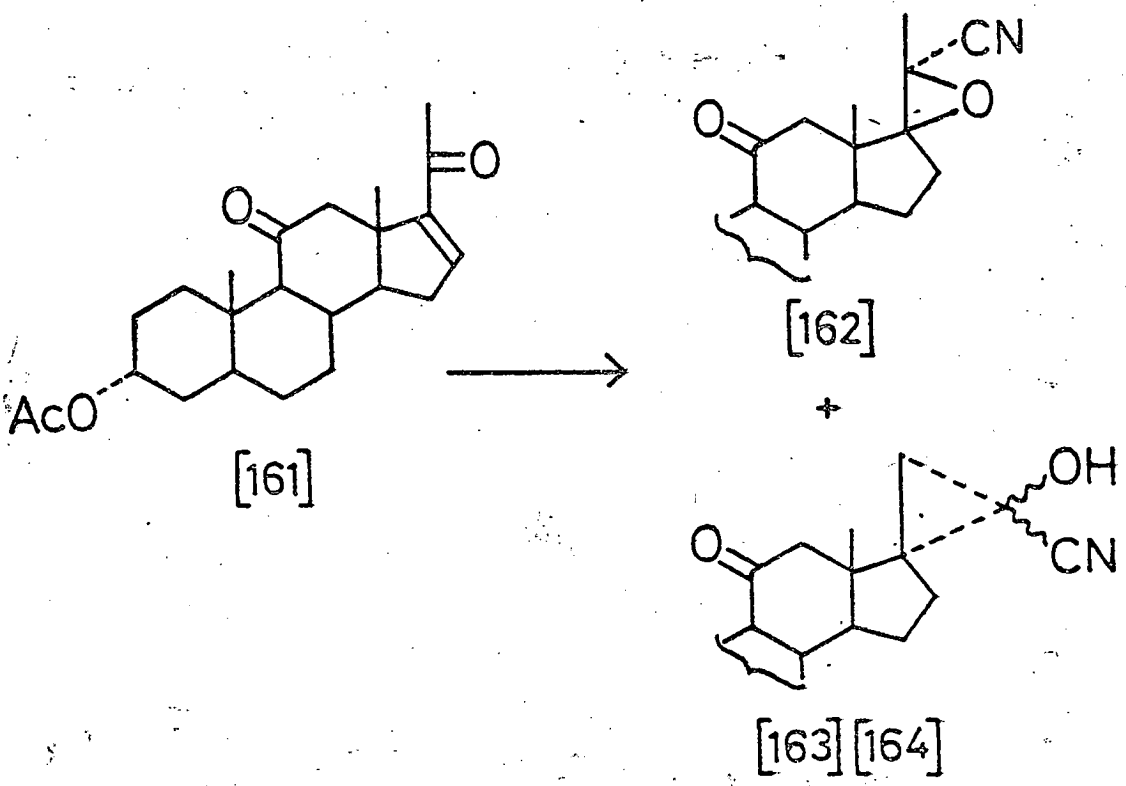
Scheme 44

No additional evidence as to the nature of the ring expanded product could be taken from the n.m.r. spectrum, the mixture being unable to be completly resolved, column chromatography, followed by thin layer chromatography showing the presence of at least two spots almost coincidental. The n.m.r. spectrum proved to be complicated and badly resolved although the mass spectrum did show a marked increase in intensity of the peak $^{m}/_{e}$ 126 from 50% of $^{m}/_{e}$ 139 in hecogenin, to 76% in the mixture, the peak assigned to the molecular ion of C-homo-hecogenin, $^{m}/_{e}$ 444 gives 20% intensity compared to $^{m}/_{e}$ 126, good evidence, with the appearance of the carbonyl absorption in the infra-red spectrum, for theformation of the C-homo steroid.

Attention was first turned to the 12-keto steroids as opposed to 11-keto steroids since the latter speces show more hindrance to reaction at the carbonyl. Herzog *et al*[71] found on reacting 3α-acetoxy-5α-pregn-16-ene-11,20-dione (161) with potassium cyanide, an epoxide (162) plus two other products had formed, these two products thought to be intermediates in a Favorskii rearrangement (163) and (164). No reaction occurred at the 11-carbonyl however. Scheme 45.

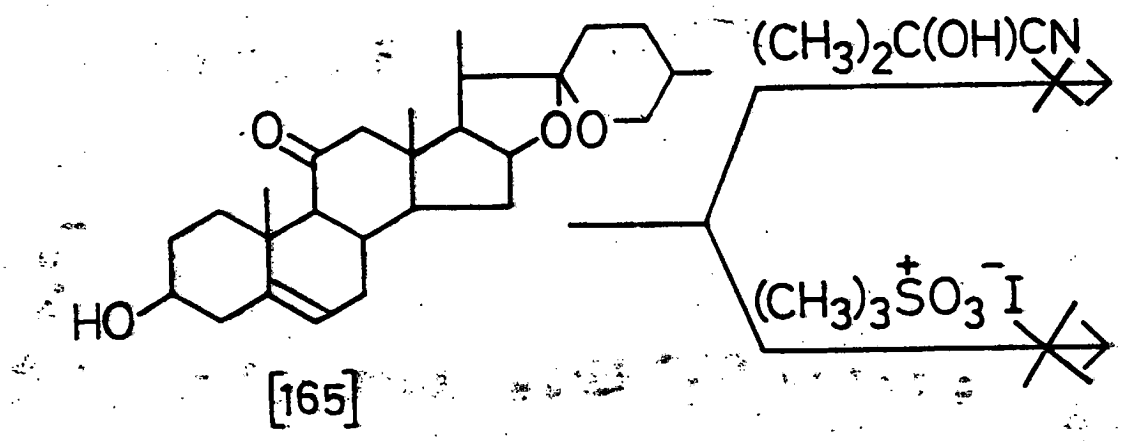
Treatment of Δ^5-11-keto-tigogenin (165) with acetone cyonohydrin under identical conditions to those for hecogenin acetate gave no reaction even with prolonged warming, the n.m.r, infra-red and mass spectra of the product being identical to those of starting material.

Steric hindrance was again illustrated in the attempted exocyclic epoxide formation by reaction of Δ^5-11-keto-tigogenin with trimethyl sulphoxonium iodide where again only starting material was recovered. Scheme 46.



Scheme 45

The successful application of the Tiffeneau-Demjanov rearrangement therefore, proved limited to the 12-keto sapogenins, the availability of the aminoalcohols being the limiting factor in the yields of homologation product, the crude C-homo-hecogenin acetate being made in 11% overall yield from hecogenin acetate via the cyanohydrins. Difficulty in purification of the products, also allowed only limited study of C-homo-hecogenin ketone ratios although the 12-keto isomer appears to formto a greater extent if not to the complete exclusion of the 12a-isomer.



[165]

Scheme 46

Experimental Procedure

Melting points were determined on a Kofler hot stage apparatus and are corrected. Infra-red spectra of carbon disulphide solutions were recorded on a Unicam S.P. 200 spectrometer. Nuclear magnetic resonance spectra of deuteriochloroform solutions were recorded on a Perkin Elmer R10 ($60MH_z$) spectrometer, an EM-360 ($60MH_z$) spectrometer or a Varian HA 100 ($100\ MH_z$) spectrometer with tetramethylsilane as an internal standard.

Merck silica gel GF_{254} was used for thin layer chromtography and the eluting system was benzene-ethanol (9:1) unless otherwise stated. The plates were developed with sulphuric acid in ethanol (1:19) spray and then heated. Alumina refers to Spence type A1 alumina of Brockman activity 2 and 5% deactivated alumina to alumina deactivated with 5% by volume of a 10% solution of acetic acid.

Mass spectrometry was carried out on an AET MS 902 instrument operated at 70eV by Mr. D. Thomas. Small samples were transferred to a quartz direct insertion probe as solutions in chloroform and the solvent was removed by evaporation.

Gas chromatography was carried out on a Perkin Elmer model 801 instrument with 6 ft all glass columns of 1/8" internal diameter. Stationary phases were the methylsilicone, OV-1 and the methylsiloxane polymer, SE-30. Various column temperatures were used and are stated in the text. The detector and injector were maintained at slightly higher temperatures than the column.

2.2 Experimental Section

A Preparation of A-homocholestanone (11)(13)

2.2.i Cholestan-3β-ol[72]

Cholesterol (12.5g) was dissolved in ethyl acetate(170ml) at 40-50°C and was hydrogenated at room temperature and pressure in the presence of 10% palladium/charcoal (1.0g) and 70-72% perchloric acid (5 drops). The hydrogen uptake was complete in 40 minutes when 50% sodium hydroxide (1 ml) was added, the catalyst was filtered off and the solvent was removed using a rotary evaporator. The resulting white solid was recrystallised from methanol to give cholestan-3β-ol (10.1g, 84%); m.p. 139-141° (lit.,[72] 140°); n.m.r. (60 MHz)τ 9.36 (C-18 methyl) 9.20 (C-19 methyl).

2.2.ii Cholestan-3-one[74](1)

Cholestan-3β-ol (6.0g) was dissolved in acetone (400ml) and 8N chromic acid (12ml) was added. After 4 minutes, excess reagents were destroyed with methanol, water (40ml) was added and the acetone was stripped off using a rotary evaporator. The product which had precipitated out was extracted into ether and the ethereal solution was washed with dilute hydrochloric acid then with water before being dried over magnesium sulphate. After filtration, the solution was evaporated to dryness leaving a white solid residue, one recrystallisation of which from acetone gave cholestan-3-one (3.69g, 51%); m.p. 125-127° (lit.,[74] 128-129°); ν_{max} 1720 cm^{-1}; n.m.r. (60 MHz)τ 9.35 (C-18 methyl), 9.00 (C-19 methyl).

2.2.iii 3-Acetoxy-3-cyanocholestane epimeric mixture[4] (3)(5)

Cholestan-3-one (1.0g) was dissolved in ethanol (7ml), benzene (4ml) and water (0.05ml), potassium cyanide (0.25g) and acetic

anhydride (0.25ml) were then added to the solution at 0°C. After stirring for 2.5 hours at 0°C, water was added and the steroid was extracted into ether. The ethereal solution was washed with water. dried over magnesium sulphate and evaporated to dryness. The colourless glass-like residue was dissolved in pyridine (3ml) and acetic anhydride (3ml) was added, the mixture was then allowed to stand at room temperature overnight. The solution was then poured into water and extracted three times with ether, the ethereal solution was washed with dilute hydrochloric acid, dilute sodium carbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness. The white solid remaining was recrystallised once from methanol to give the epimeric mixture of 3-acetoxy-3-cyanocholestanes (0.56g, 52%); m.p. 123-125° (lit.,[4] 123-126°); ν_{max} 1755, 1228, 1033 cm^{-1}.

2.2.iv 3β-acetoxy-3α-cyano-cholestane[9] (3)

To a solution of cholestan-3-one (1.0g) in ethanol (10ml) was added freshly distilled acetone cyanohydrin and triethylamine (2ml). The mixture was then refluxed for 3 minutes before being poured into water, the precipitate formed was extracted into ether. Acetylation was carried out as in 2.2.iii with pyridine (3ml) and acetic anhydride (3ml) giving the epimeric pair of acetylated cyanohydrins (0.86g, 73%); m.p. 122-126° (lit., 123-126°). Three recrystallisations from methanol yielded the pure 3β-acetoxy-3α-cyano-cholestane (0.23g, 21%); m.p. 117-122° (lit., 123-126,[4] 125-126[9]); ν_{max} 2900, 2100, 1720, 1245 cm^{-1}.

2.2.v a. Epimeric mixture of 3-aminomethyl-cholestan-3-ols (7)(9)

3-Acetoxy-3-cyanocholestane (1.0g) was dissolved in anhydrous ether (15ml) which was added dropwise to a slurry of lithium aluminium hydride (1.0g) in refluxing anhydrous ether (45ml). After addition was complete, the reaction mixture was refluxed for a further

hour before the excess litium aluminium hydride was destroyed by the careful addition of dilute sulphuric acid. The ether layer was washed with 10% sodium hydroxide, dried over magnesium sulphate, filtered and evaporated to dryness to leave a white solid residue (618mg, 61%).

b. The acetonides of 3-aminomethyl-cholestan-3-ols (140)(141)

The aminomethyl cholestanols (618mg) were dissolved with warming in acetone (8 ml) and the acetone was slowly distilled off until a white crystilline solid began to separate out. The reaction mixture was then cooled and the solid was filtered off and recrystallised from acetone to give 3-(5'-spiro-2',2'-dimethyloxazolidinyl)-cholestane (383mg, 62%); m.p. 146-148° (lit.,[5,9] 145-146°); ν_{max} 840, 820 cm^{-1}; n.m.r. (60 MHz) τ 9.38 (C-18 methyl) 9.22 (C-19 methyl), 8.65 (geminal methyls), 6.94 (2 protons α to imino).

2.2.vi A-Homocholestanone[9] (11)(13)

The epimeric mixture of acetonides (0.2g) was dissolved in a mixture of glacial acetic acid (3.75ml) and ether (1.25ml) and the solution was cooled to -10°C. A solution of sodium nitrite (0.5g) in water (2.5ml) was then added dropwise, the temperature never being allowed to rise above 5°C. After all the sodium nitrite solution had been added, the mixture was stirred for 3 hours at 0°C. The mixture was then poured into water and the precipitated steroid was extracted three times with ether, the combined extracts were washed with sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness leaving a pale brown oil. Chromatography on 5% deactivated alumina (20g) and elution with petroleum-ether (40-60°) gave a white crystalline material (0.15g). One recrystallisation from ethanol gave

the approximately 50:50 mixture of A-homocholestan-3-one (11) and A-homocholestan-4-one (13) (0.12g, 69%); m.p. 80.82° (lit.,[4,9] 85-87°, 86-88°); ν_{max} 1700 cm^{-1}; n.m.r. (100MHz) τ 9.346 (C-18 methyl). 9.201 (2 peaks; C-19 methyls), 9.171, 9.106 (C-26 and C-27 methyls), 9.130, 9.074 (C-21 methyl).

B Preparation of C-homohecogenin acetate via the cyanohydrins

2.2.vii 12-Cyano-12-hydroxy-tigogenin acetates (143)(144)

Hecogenin acetate (0.5g) was suspended in acetone cyanohydrin (7ml) and ethanol (7ml) and triethylamine (5 drops) were added. The steroid completely dissolved on warming followed immediately by the formation of a heavy precipitate. Warming was continued for a further 5 minutes, the reaction mixture was then cooled and the product was filtered off and washed with hot ethanol then dried in a stream of air to give the epimeric mixture of 12-cyano-12-hydroxy-tigogenin acetates (0.51g, 96%); m.p. 268-272° (lit.[58], 271-275°); ν_{max} 3450, 2930, 1735, 1050, 1035, 980, 898 cm^{-1}; mass spectrum m/e 499 (M^+, 2%).

2.2.viii Hydrogenation of 12-cyano-12-hydroxy-tigogenin acetates[75]

a. Adams catalyst with perchloric acid

The 12-cyano-12-hydroxy-tigogenin acetates (50mg) were dissolved in ethyl acetate (10ml) and hydrogenated at room temperature under one atmosphere of hydrogen in the presence of Adams Catalyst ($PtO_2.H_2O$, 100mg) and perchloric acid (2 drops). No more hydrogen was taken up after 4 hours when the catalyst was filtered off and the solution was evaporated to dryness leaving a gum (54mg). The t.l.c., infra-red and mass spectra of the product showed it to be unreacted cyanohydrins with traces of two other components.

b. Fresh Adams catalyst in acetic acid

The 12-cyano-12-hydroxy-tigogenin acetates (300mg) were dissolved in acetic acid (50ml) and hydrogenated at room temperature under atmospheric pressure of hydrogen in the presence of Adams catalyst (100mg) from a fresh batch. After stirring overnight, the catalyst was filtered off, water was added to the mixture and the product was extracted into ether. The ether extracts were combined, washed with 5% sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness leaving a yellow-brown solid (268mg). T.L.C. showed two spots, the minor one of which corresponded to hecogenin acetate, n.m.r. (60 MHz) τ 9.13 (C-18 and C-19 methyls), 7.98 (C-3 acetate); mass spectrum $^{m}/_{e}$ 503 (M^+, 1.5%), $^{m}/_{e}$ 473 ($M-CH_2NH_2$, 15%) 12-aminomethyl-12-hydroxy-tigogenin acetate; $^{m}/_{e}$ 472 (M^+, 13%) hecogenin acetate.

2.2.ix C-Homohecogenin acetate (148)

The crude 12-aminomethyl-12-hydroxy-tigogenin acetates (100mg) were dissolved in acetic acid (20ml) and the solution was stirred at 0°C withthe dropwise addition of sodium nitrite (0.25g) in water (1.25ml). The reaction mixture was stirred for 2 hours at 0°C after addition was complete, then at room temperature for a further 2 hours. The solution was then poured into water and extracted into ether. The ether layer was washed with 5% sodium bicarbonate solution then with water, dried over magnesium sulphate, filtered and evaporated to dryness leaving a yellow viscous gum (62mg). T.L.C. showed one spot; ν_{max} 1697 cm^{-1}; n.m.r. (60 MHz) τ 9.13 (C-18 methyl), 8.74 (C-19 methyl), 7.98 (C-3 acetate) mass spectrum, $^{m}/_{e}$ 486 (M^+, 11%), $^{m}/_{e}$ 456 (54%), $^{m}/_{e}$ 414 (18%), $^{m}/_{e}$ 372 (35%), $^{m}/_{e}$ 342 (71%), $^{m}/_{e}$ 139 (39%), $^{m}/_{e}$ 126 (100%), 12-keto-C-homohecogenin acetate.

C Preparation of C-homohecogenin via the exocyclic epoxides of hecogenin

2.2.x 12α-12'-Epoxy-12β-methyl-tigogenin[67] (158)

Hecogenin acetate (1.0g) was added to a stirred slurry of sodium borohydride (1.5g) and trimethyl suphoxonium iodide (4g) in dimethyl formamide (100ml) at room temperature. After 16 hours, the mixture was poured into water and the resulting precipitate was filtered off, washed with water, then dried in vacuo. One crystallisation from methanol gave pure 12α,12'-epoxy-12β-methyl tigogenin (91mg, 97%); m.p. 240-242° (lit,[64] 240-242°); ν_{max} 2810 cm^{-1}, no peaks corresponding to a carbonyl but the C-O-C ether bands of the E- and F-rings mask the peaks from the exocyclic epoxide; n.m.r. (60 MHz) τ 9.16 (C-18 methyl), 9.06 (C-19 methyl), 7.45 (C-12' methylene); 7.45 (C-12' methylene); mass spectrum, M^+, m/e 444 (17%).

2.2.xi 12β-Azidomethyl-12α-hydroxy-tigogenin (160)

12α,12'-Epoxy-12β-methyl-tigogenin (75mg) in dimethyl formamide (20ml) was heated under reflux for 3 hours with sodium azide (1g) and boric acid (1g). A suspension formed during this time, water was then added and the precipitate was filtered off, washed with water and dried in vacuo giving 12β-azidomethyl-12α-hydroxy tigogenin as an off-white solid (83mg, 100%). T.L.C. showed one spot; ν_{max} 2910 cm^{-1}; n.m.r. (60MHz) τ 9.20 (C-18 and C-19 methyls), 6.68 (C-12' methylene).

2.2.xii C-Homohecogenin

12β-Azidomethyl-12α-hydroxy-tigogenin (1.0g) in acetone (60ml) was treated with concentrated hydrochloric acid (6.5ml) and stirred during gradual addition (~5 minutes) of zinc powder (7g). After approximately 45 minutes, when gas evolution had ceased, the mixture was filtered to remove the zinc powder which was washed well

with acetone. The combined acetone washings and reaction mixture were concentrated to small volume. Fresh acetone (30ml) and water (200ml) were added and the solution was extracted twice with ether. The acetone-water layer was then cooled below 5°C and sodium nitrite (3g) added. After 3 hours below 5°C, the reaction mixture was allowed to warm to room temperature and the acetone was removed in vacuo. The precipitate formed was extracted into ethyl acetate, the organic layer was removed, dried over magnesium sulphate, filtered and evaporated to dryness leaving a yellow glass (43mg). T.L.C. showed two main spots and two minor spots; ν_{max} 1707cm^{-1}; mass spectrum M$^+$, $^m/_e$ 430 (30%) hecogenin; ν_{max} 1697cm^{-1}; mass spectrum, M$^+$, $^m/_e$ 444 (15%) C-homo-hecogenin; calculated for $C_{28}H_{44}O_4$ 444. 323941, found 444. 323935, $^m/_e$ 139 (100%), $^m/_e$ 126 (76%).

D Miscellaneous Reactions

2.2.xiii Reaction of Δ^5-11-keto-tigogenin (165) with acetone cyanohydrin

The reaction was carried out as in 2.2.vii with Δ^5-11-keto-tigogenin (0.5g) and acetone cyanohydrin (7ml). No precipitate was formed on warming, even after 1 hour. Addition of water precipitated a solid which was filtered off, washed with water and dried in vacuo (483 mg). T.L.C. showed one spot of same polarity as Δ^5-11-keto-tigogenin; ν_{max} 1705cm^{-1}; n.m.r. (60MHz) τ 9.26 (C-18 methyl), 8.76 (C-19 methyl), ^{5}-11-keto-tigogenin; mass spectrum, M$^+$, 428 (34%).

2.2.xiv Reaction of Δ^5-11-keto-tigogenin with trimethyl sulphoxomium iodide

The reaction was carried out as above, 2.2.x., with Δ^5-11-keto-tigogenin (1.0g), sodium borohydride (1.5g) and trimethyl sulphoxonium iodide (4g) in dimethylformamide (100ml). Addition of water to the

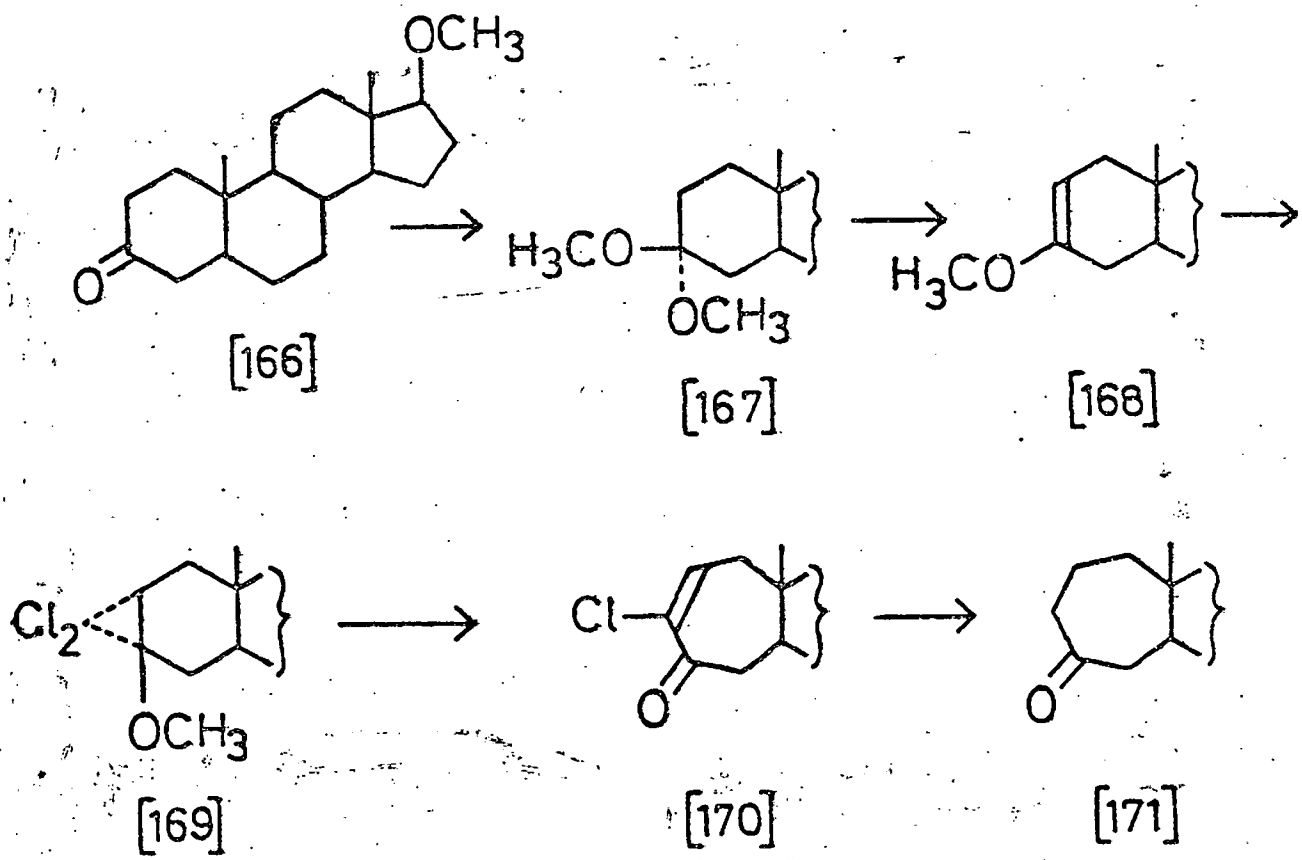
reaction mixture precipitated a solid which did not extract into ether but formed an emulsion. Chloroform extracted the product, the chloroform layer dried over magenesium sulphate, filtered and evaporated to dryness leaving a white solid (1.0g). The t.l.c., infra-red and n.m.r. spectra were identical to those of Δ^5-11-keto-tigogenin starting material.

3.1 Ring Expansions with carbene addition reactions

Because of the reactive nature of carbenes,[76,80,81] they provide a facile route for the introduction of an extra carbon atom into the steroidal ring system. Suitable substrates were however required to accommodate the strongly basic conditions under which the carbenes are generated.[82,83] They need to be unaffected themselves by base but lend themselves to subsequent rearrangement. Following the work of Levisalles *et al.*[15] in making a methyl enol ether of cholestane, the 3,3-dimethoxy-cholestane[77] (21) was prepared by reaction of cholestane-3-one (19) with methanol and concentrated hydrochloric acid catalyst. Pyrolysis at 220°C in xylene[78] of the 3,3-dimethoxy steroid then furnished the required 3-methoxy-cholest-2-ene (23) in an overall yield of 69% based upon the starting ketone. The addition of the carbene, generated from chloroform with potassium tertiarybutylate to the steroidal olefin could be followed by the disappearance of the olefinic triplet centred around 5.50 in the n.m.r. spectrum due to the single proton at C-2 in the substrate (23). The cyclopropane product (24) was made in 63% yield, however, the yields for the rearrangement step found by Levisalles could not be matched, treatment with silver acetate in acetic acid under reflux for 40 hours giving only 37% of 3-chloro-A-homocholest-2-en-4-one (26) after purification on a silica gel column, compared to a claimed yield of 56%. Hydrogenation of the 3-chloro-2-olefin in benzene with 10% palladium on charcoal afforded the saturated ring-A expanded ketone, A-homocholestan-4-one (13) showing an absorption in the carbonyl region of the infra-red spectrum at 1700cm^{-1} compared to 1710cm^{-1} for the starting material. The C-19 methyl signal in the n.m.r. spectrum shows the expected upfield shift[79] from τ 9.0 in cholest-3-one to τ 9.201 due to loss of net deshielding. The triplet due to the olefinic proton in

3-chloro-A-homocholest-2-en-4-one centred around τ 3.29 was now gone as had the chlorine atom during the hydrogenation of the double bond.

Preparation of the previously unreported 17β-methoxy-A-homo-androstan-4-one (171) by the same process proceeded in good yields giving a 75% carbene addition. Starting material was 17β-methoxy-androstan-3-one (166) made from 17β-hydroxy-androstan-3-one (2) by a Purdie methylation.[84] The carbonyl band of the product appeared at 1702cm^{-1} in the infra-red spectrum and an upfield shift relative to starting material, of the C-19 methyl signal in the n.m.r. spectrum occurred from τ 8.98 in the 17β-methoxy-androstan-3-one, to τ 9.20 in its homologue. Scheme 47.



Scheme 47

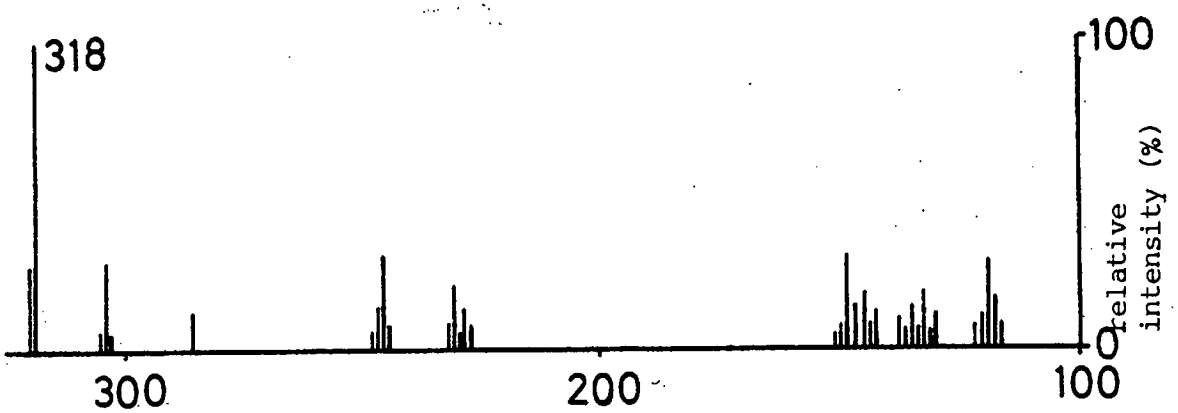


fig. 4 Mass spectrum of 17β-methoxy-A-homoandrostan-4-one(171)

The results are tabulated. Table 8.

Compound	infra-red	n.m.r.		G.L.C. 250°C SE-30	
	C=O stretch cm^{-1}	C-18 methyl (τ)	C-19 methyl (τ)	retention times (mins)	Rf starting material: Rf product
Cholestanone	1710	9.35	9.00	24.8	7:5
A-homocholestan-4-one	1700	9.35	9.201	34.8	
17β-methoxyandrostan-3-one	1708	9.23	8.98	6.0	7:5
17β-methoxy-A-homoandostan-4-one	1702	9.25	9.20	8.4	

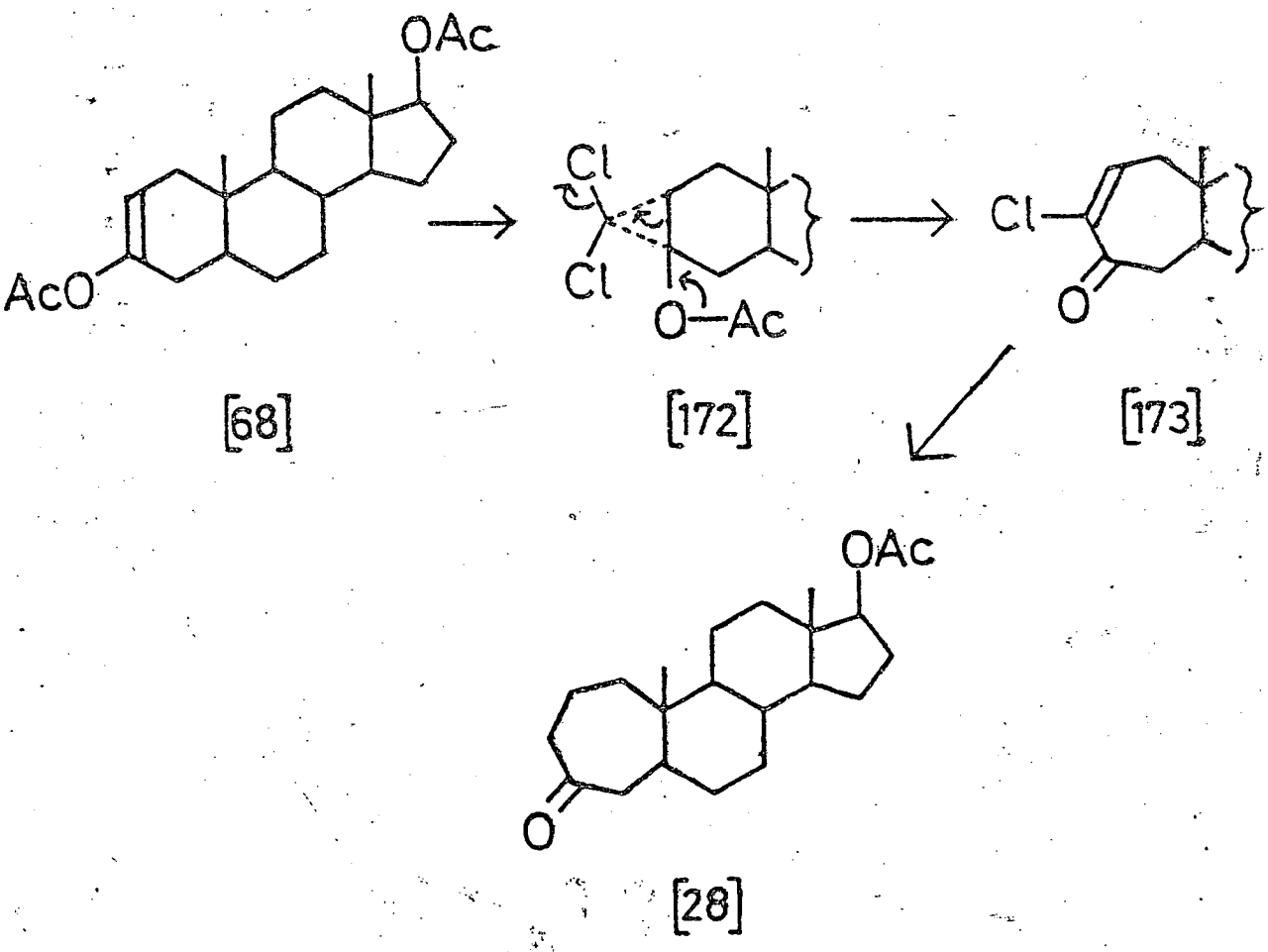
Table 8

It can be seen from the retention times quoted in table 8 that addition of one extra carbon to ring-A increases the time by the same proportion, compared to starting material, in both cases.

The mass spectrum of 17β-methoxy-A-homoandrostan-4-one fig.4 showed the molecular ion at $^{m}/_{e}$ 318 which was also the parent ion, further important peaks appeared at $^{m}/_{e}$ 304 (27%) and $^{m}/_{e}$ 286 ($-CH_3OH$, 12.5%). Exact mass measurements of the products of all five stages differed by no more than five parts per million from that calculated for the empirical fomula in any one case.

The limitation of substrate for carbene addition to those unaffected by basic conditions was overcome by use of phenylmercuric carbene precursors studied at some length by Seyferth and various co-workers.[27] Their advantage of decomposing under neutral conditions allowed Stork *et al.*[18] to use an enol acetate as substrate for carbene

addition leading to a ring-A expanded steroid. Following this work, the enol acetate of androstan-3-one (2), 3,17β-diacetoxy androst-2-ene[85,86] (68), was prepared in quantitative yields by reaction of androstan-3-one with acetic anhydride and 72% perchloric acid catalyst. Generation of the dichlorocarbene by decomposition of phenyl (bromo-dichloromethyl) mercury in refluxing benzene gave 64% of the addition product (172) after 4 hours, the course of the reaction was followed

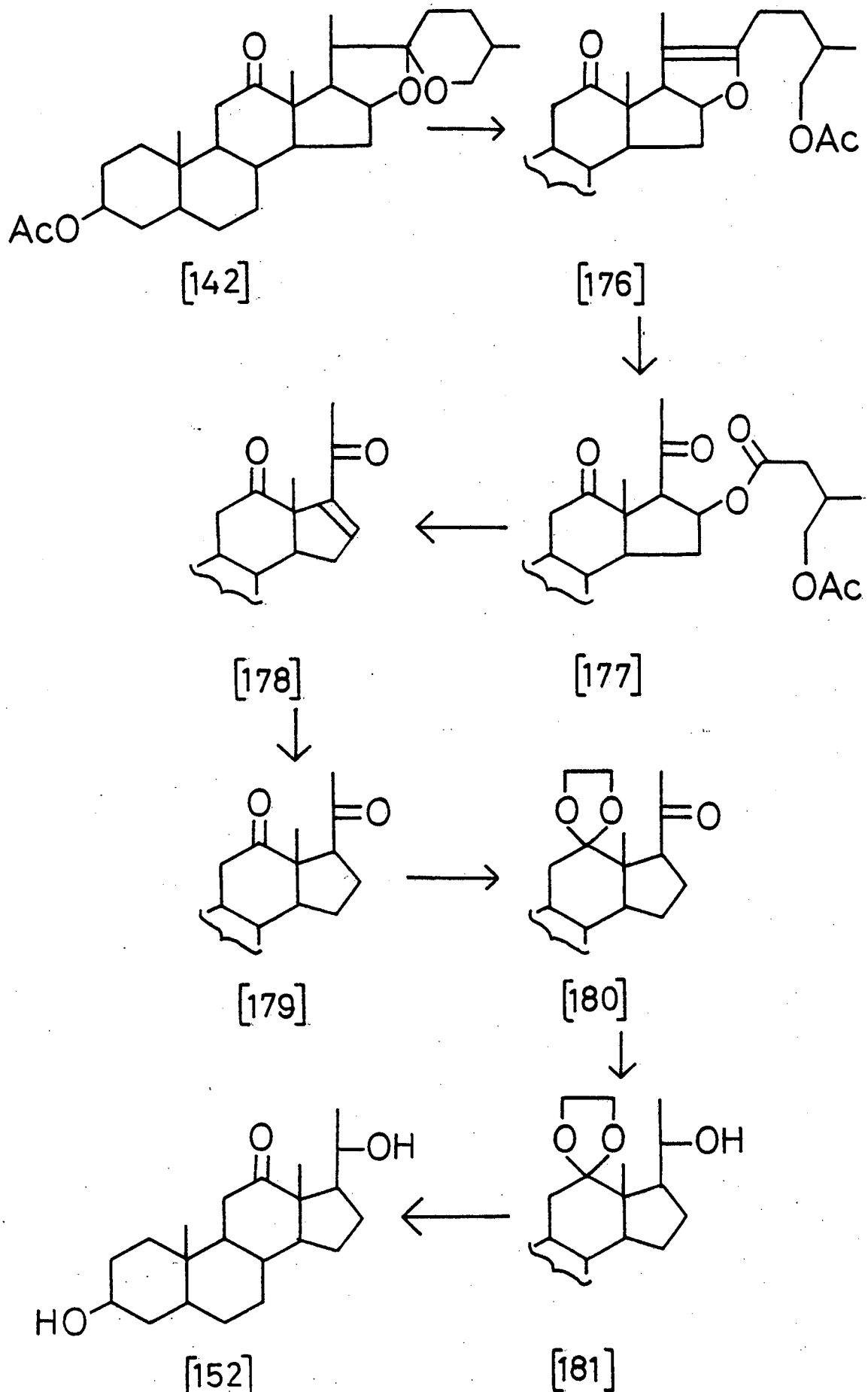


[68] [172] [173] [28]

Scheme 48

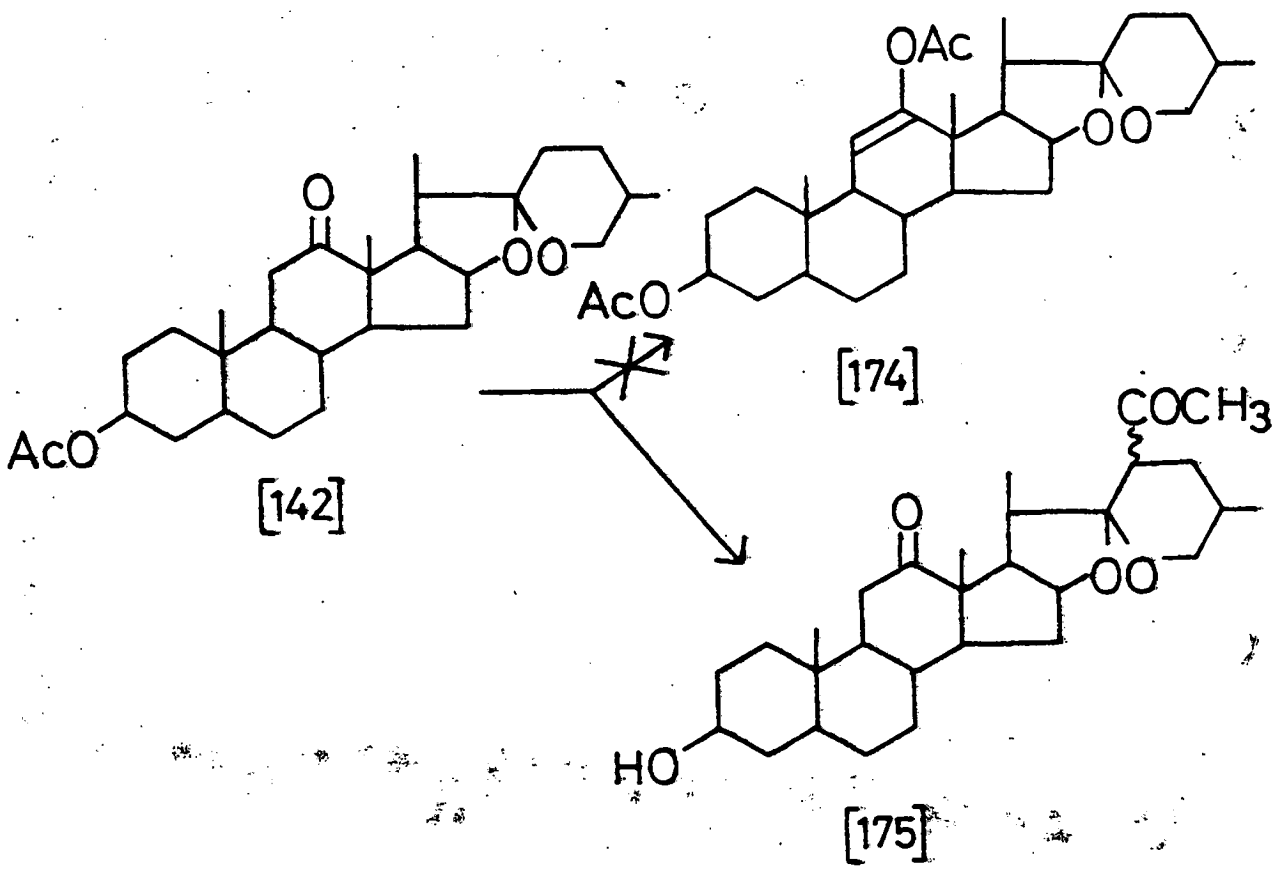
by disappearance of the olefinic proton peak of the starting material in the n.m.r. spectrum. After 12 hours, complete loss of olefinic peaks showed the reaction to have gone to completion, recrystallisation of the product giving thepure dichlorocyclopropane derivative (172) which readily rearranged with base, Scheme 48, to give the unsaturated ring-A expanded ketone (173). Hydrogenation furnished the final product, 17β-acetoxy-A-homoandrostan-4-one (28).

The enol acetate of hecogenin acetate (174) would have been an ideal starting material for this reaction route leading to the ring-C expanded homologue. However, attempted enol acetylation by reaction of hecogenin acetate with acetic anhydride and perchloric acid as catalyst with slow distillation to small volume produced none of the required enol acetate. Scheme 49. Instead, basic hydrolysis of the product gave 23ξ-acetyl-hecogenin (175), the infra-red spectrum of which showed absorptions at 1010, 955, 935 and 900cm^{-1} indicative of 23-substituted sapogenins[87]. Degredation of the E- and F-rings[88,89] was undertaken in the hope that a simpler skeletal structure would allow the formation of a Δ^{11}-12-acetate grouping. Scheme 50. The first step, leading to ψ-hecogenin(176) was carried out according to Cameron et al.[87] using n-octanoic acid and acetic anhydride which increased the yields produced in the original method of Marker who used acetic anhydride alone. ψ-Hecogenin gave no reaction at the 12-ketone under both sets of conditions for enol acetylation. Further breakdown by oxidation to 3β-acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnane-12,20-dione (177) then by treatment with Spence grade H alumina gave good yields of 3β-acetoxy-pregn-16-ene-12,20-dione (178). Enol acetylation of this compound again gave no reaction at C-12 but formed a triacetate shown by Wall et al.[90] to be 3β,16β,20-triacetoxypregn-17(20)en-12-one (184),



[142] [176] [177] [178] [179] [180] [181] [152]

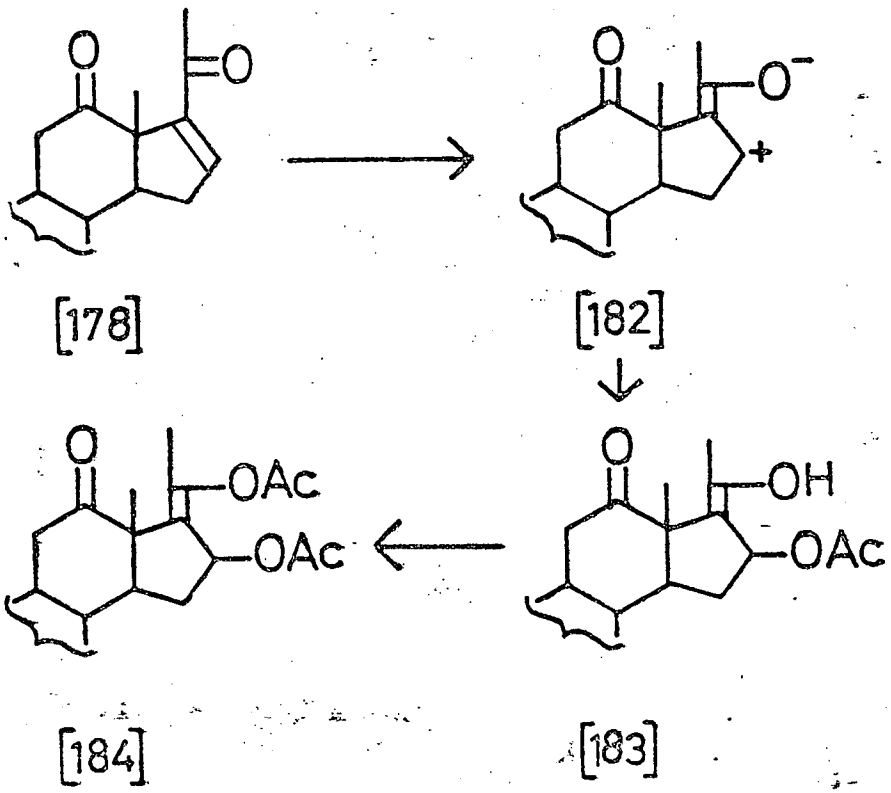
Scheme 50



Scheme 49

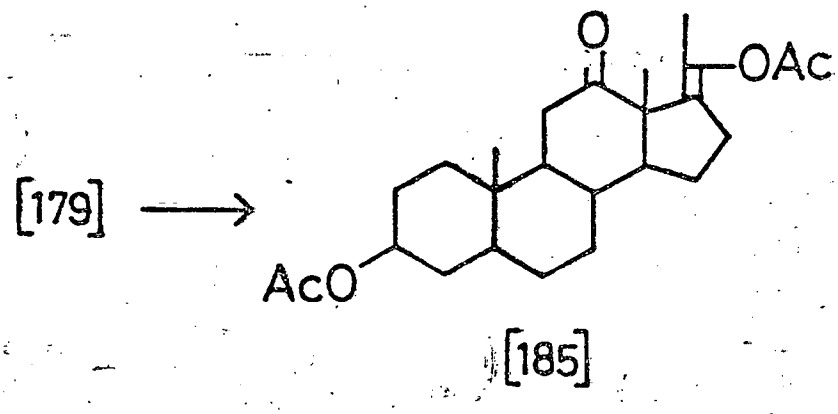
acetylation at C-16 being due to the existance of a partial positive charge at C-16 under these conditions. Scheme 51. The product is thought to form via a hemi-acetal intermediate at the 12-carbonyl.[91,92] The infra-red spectrum shows the presence of the enol acetate at 1663cm^{-1}. Further peaks at 1730 and 1710 account for the other two acetates and the C-12 carbonyl respectively. The n.m.r. spectrum shows the three acetate methyls at τ7.93 (C-20 acetate), and τ8.00 (C-3 and C-16 acetates).

Enol acetylation of the saturated dione (179) formed by hydrogenation of the 3β-acetoxy-5α-pregnane-12,20-dione, gave only the $\Delta^{20(17)}$-20-acetate (185), Scheme 52, with no reaction at C-12. This is in line with the results of Barton et al.[93] This was accomplished



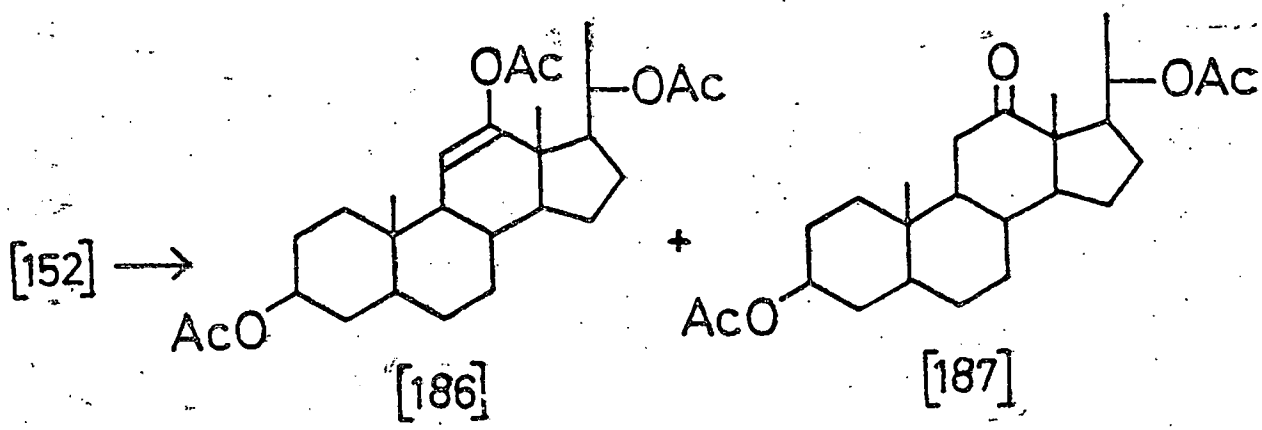
Scheme 51

only with acetic anhydride and toluene-4-sulphonic with slow distillation, and not with perchloric acid catalyst.



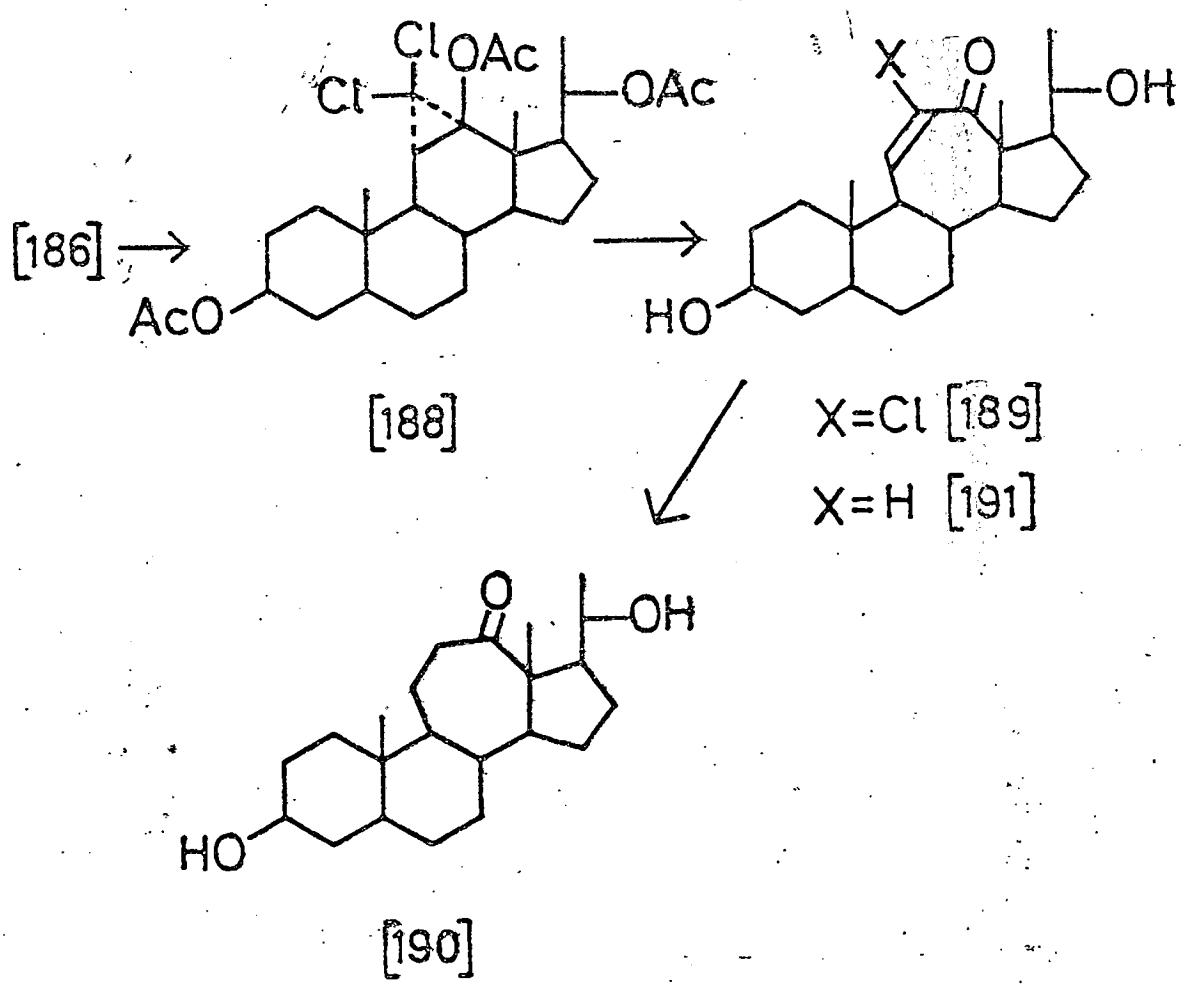
Scheme 52

Protection of the 12-ketone by selective ketal formation[94] allowed hydrogenation[95,96,97,98] of the 20-carbonyl. Removal of the protecting group[99] afforded 3β,20β-dihydroxy-pregnan-12-one (152). Reaction with perchloric acid catalyst was again unsuccessful, however, acetic anhydride and toluene-4-sulphonic acid formed approximately 50% of the required 3β,12,20β-triacetoxy-5α-pregn-11-ene (186) in the crude reaction mixture. Scheme 53. The n.m.r. spectrum of the mixture showed the acetate peaks at τ8.02, τ7.98 due to the C-20 acetate and C-3 acetate respectively, and τ7.90 about 50% as intense as the other two and due to the enol acetate. A doublet due to the single olefinic proton on C-11 appears centred around τ4.78. The mass spectrum shows a low intensity molecular ion at $^{m}/_{e}$ 460 and the molecular ion of the diacetylated ketone, 3β,20β-diacetoxy-pregn-12-one (187), at $^{m}/_{e}$ 418. This proved a suitable substrate for carbene addition, treatment of the crude mixture with phenyl (bromodichloromethyl) mercury in refluxing benzene for 48 hours resulting in the formation of the dichlorocyclopropane derivative (188), the configuration being assigned on previous evidence for α-attack by the carbene. Scheme 54.



Scheme 53

The n.m.r. spectrum of the brown solid product now showed no evidence for an olefinic proton but a C-Cl absorption appeared in the infra-red spectrum at 720cm^{-1}. After 3 days of stirring at room temperature in ethanolic potassium hydroxide and pyridine, a pale brown solid was produced showing a carbonyl absorption at 1695cm^{-1} in the infra-red, the n.m.r. spectrum of which displayed an olefinic proton signal as a broad peak centred around τ5.34 due to the single proton at C-11 in the rearrangement product, 3β, 20β-dihydroxy-12-chloro-C-homopregn-11-en-12a-one (189). Hydrogenation of this unsaturated ketone gave the



Scheme 54

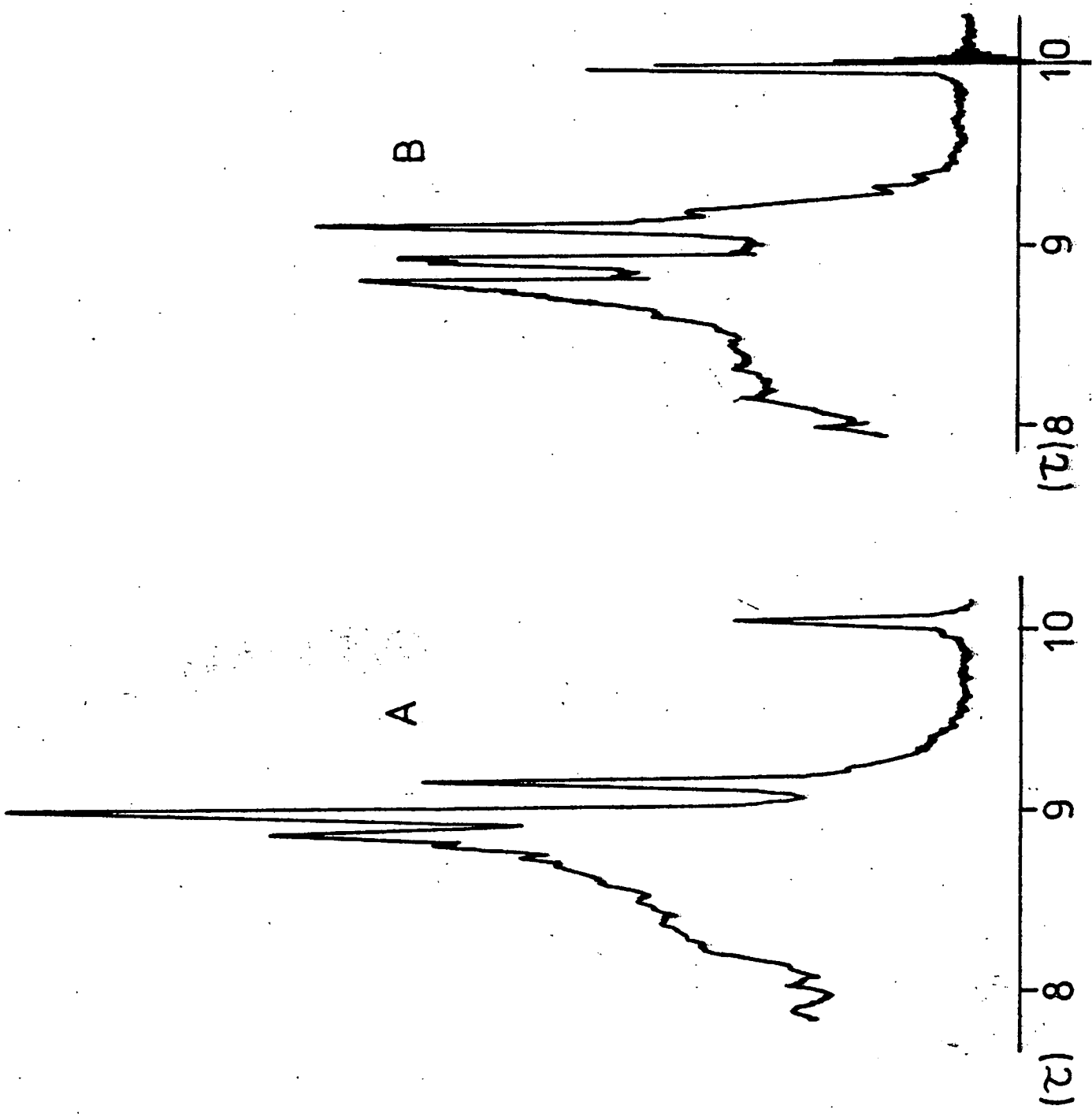
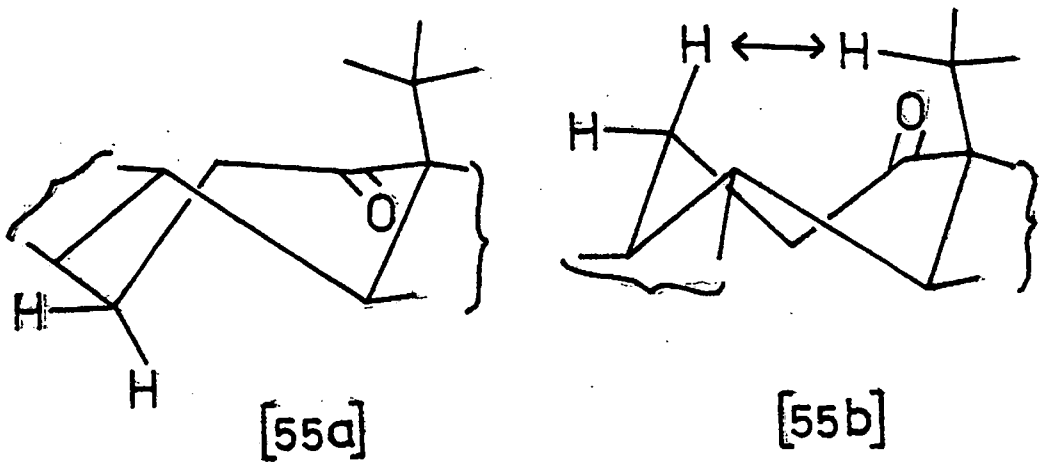


fig.5. n.m.r. spectra of 3β,17β-dihydroxy-pregn-12-one(152) A and 3β,17β-dihydroxy-C-homopregn-12a-one(190) B

final product, 3β,20β-dihydroxy-C-homopregn-12a-one (190). T.L.C. of the crude reaction mixture showed two overlapping spots one of which corresponded to the unexpanded starting material (152). Recrystallisation from acetone gave pure starting material, the required product remaining in the mother liquors. T.L.C. of the mother liquors still showed trace amounts of starting material substantiated by the mass spectrum which gave a peak at $^{m}/_{e}$ 334 corresponding to the molecular ion of 3β,20β-dihydroxy pregn-12-one. However, peaks also appeared at $^{m}/_{e}$ 348 (13%) and $^{m}/_{e}$ 333 (27%) due to the C-homo adduct. This is analogous to the unexpanded material which shows the molecular ion at $^{m}/_{e}$ 334 (13%) and a peak at $^{m}/_{e}$ 319 (M^{+} -15, 16%). Also present in the mass spectrum was a peak at $^{m}/_{e}$ 346 (20%) due to incomplete hydrogenation of the Δ^{11}-12-chloro ketone (189). This was however, present only in small amounts since the n.m.r. spectrum showed no olefinic functions. Exact mass calculations for $^{m}/_{e}$ 348 gave 348.265370 compared to 348.266430 calculated for $C_{22}H_{36}O_3$, an error of less than 3 p.p.m. For $^{m}/_{e}$ 346 was found 346.250648 compared to 346.250781 calculated for $C_{22}H_{34}O_3$, an error of less than 1 p.p.m. The n.m.r. spectrum shows the expected downfield shift of the C-19 methyl signal compared to the six-membered species, the single peak due to C-19 methyl and one of the two C-21 methyl signals at τ8.92 having become two peaks at τ8.92 and τ8.90, the latter being the new position of C-19 methyl. The C-18 methyl signal now appears at τ9.10 opposed to τ9.08 fig. 5. These small changes in the spectra reflect the relatively slight differences in the relationship of the methyl groups, and the carbonyl on going from the six-membered ketone to the 12a-ring-expanded ketone. As for hecogenin acetate and C-homotigogenin acetate, the conformer 55a will exist preferentially due to steric interactions of the β-proton at C-11 and the protons of



[55a] [55b]

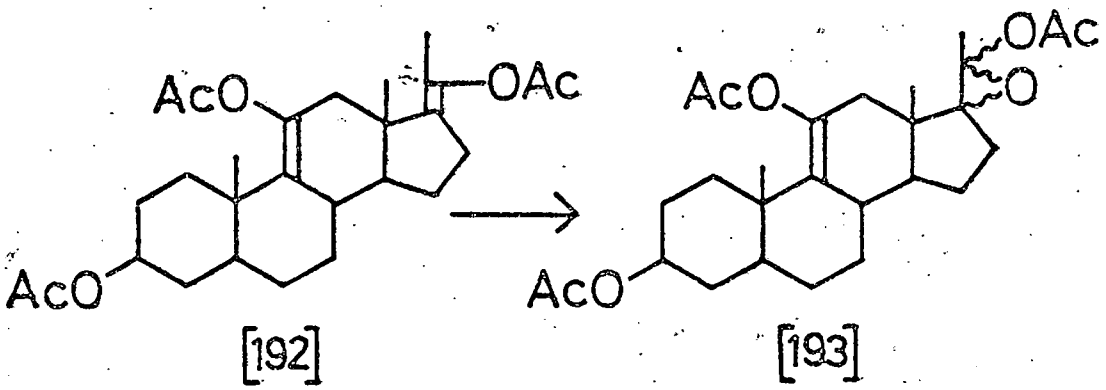
Extreme conformers of 3β,20β-dihydroxy-C-homopregn-12a-one(190)

Scheme 55

the C-18 methyl in 55b, that is to say, the conformer relating more closely to the unexpanded ketone will be in abundance. Scheme 55 .

The infra-red spectrum shows the carbonyl stretch at 1695cm^{-1} in contrast to 1703cm^{-1} for 3β,20β-dihydroxy-pregnan-12-one (152), the lower frequency being in line with comparisons of other expanded and unexpanded ring carbonyls.

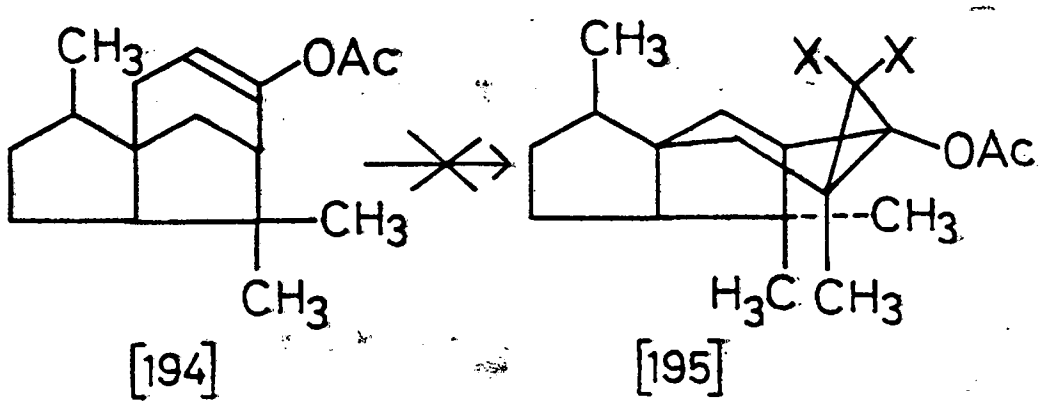
The alternative ring-C ketone available for enol acetylation and hence carbene addition is that at C-11. Enol acetylation of this carbonyl gives a $\Delta^{9(11)}$ enol acetate[100](192). This double bond has been shown to be unreative, Kritchevsky et al.[101] forming only the 17:20 mono epoxide (193) by reaction of the dienol acetate (192) with perbenzoic acid. Although Hirschmann and Wendler[102] found epoxidation to take place at $\Delta^{9(11)}$ under more vigorous conditions there was still a differential reaction of the two enol acetates ascribed to the hindrance of the $\Delta^{9(11)}$ bond resulting not only from the steric influence of the two angular methyls but also from the 11-acetoxy group. Scheme 56 .



Scheme 56

Carbene addition reactions are also adversely affected by certain steric environments shown by the enol acetate derived from

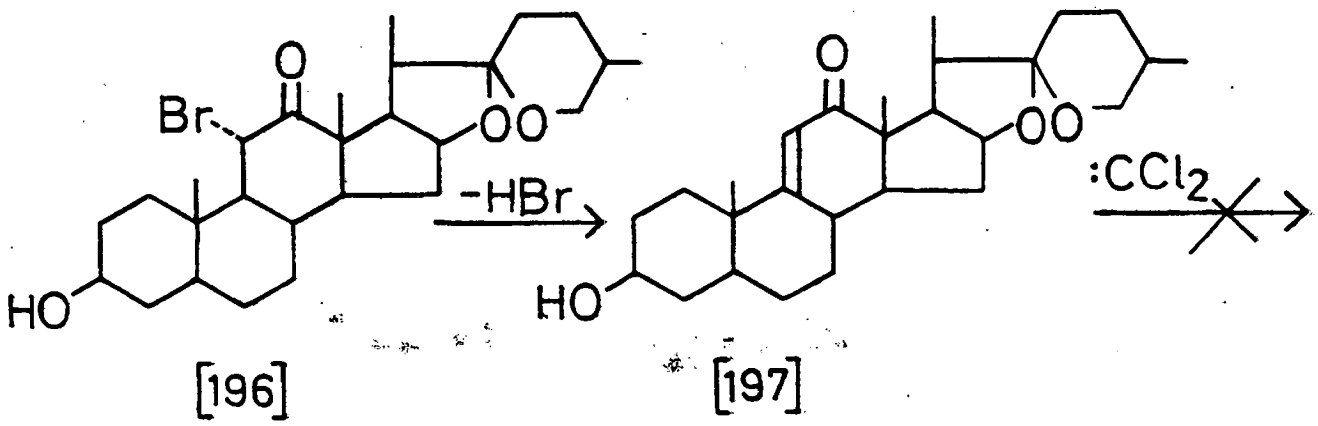
cedrene (194) which does not react with phenyl tribromomethyl mercury presumably because of the strong steric hindrance between the methyl group on the cyclopropane ring and one of the gem dimethyl groups in the eventual adduct (195) and the transition state leading to it[18] Scheme 57 .



Scheme 57

α-Bromination to the 12-ketone of hecogenin[103,104,105] followed by dehydrobromination[104] led to the $\Delta^{9(11)}$ αβ-unsaturated ketone. (197) This olefin is now free of any hindrance due to an acetoxy group, however, the unreactivity of this double bond was still in evidence as shown by the failure of phenyl (bromodichloromethyl) mercury to add a carbene. The product showed identical spectra to $\Delta^{9(11)}$ hecogenin, the n.m.r. spectrum having an olefinic proton peak at τ 4.27 indicative of the lack of reaction. Scheme 58 .

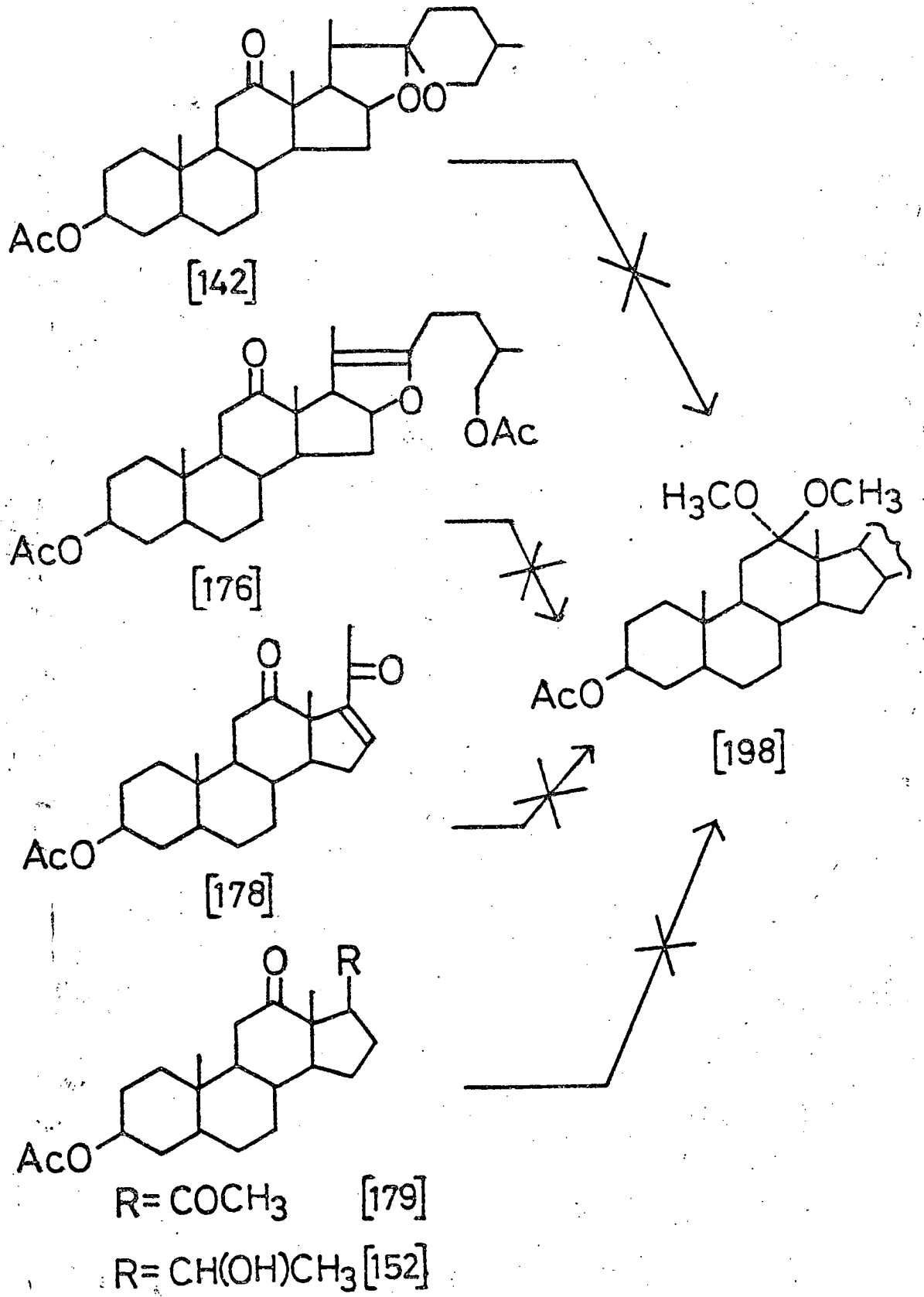
This obvious hindrance rendered it futile to attempt reaction of dichlorocarbene with the $\Delta^{9(11)}$ enol acetate in which the double bond would show increased hindrance from the 11-acetoxy group. This left suitable $\Delta^{11(12)}$ speces as the only possible substances for attack by carbenes and hence to ring expansion.



Scheme 58 ·

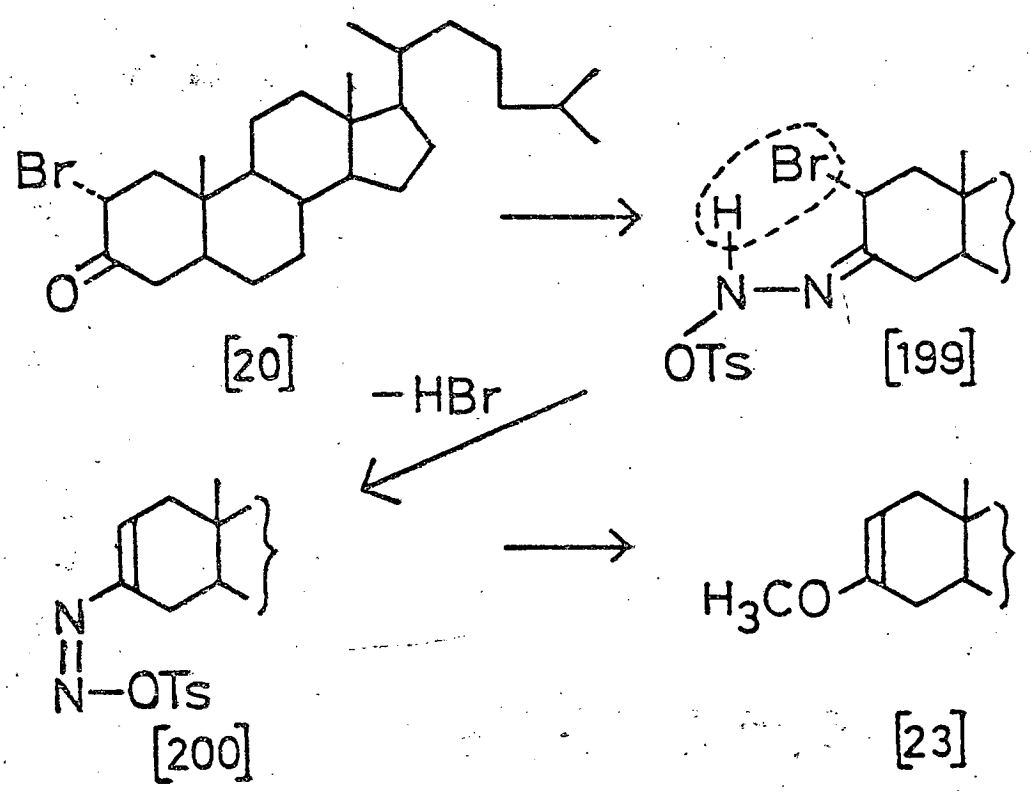
Attempts were therefore made to form suitable $\Delta^{11(12)}$ enol ethers. Attempted formation of the 12,12-dimethoxy adduct of hecogenin acetate (198) which would have led to the Δ^{11}-enol methyl ether by pyrolysis, showed that this compound could not be prepared, the infra-red spectrum indicated that strong carbonyl absorptions were still present even after refluxing the methanolic reaction mixture with concentrated hydrochloric acid. A similar lack of success was met with for the same reaction with some of the simpler steroids derived from hecogenin acetate Scheme 59 , and although 3β-hydroxy-pregna-12;20-dione (179) formed a ketal protecting group Scheme 50 (180), the resulting 3β,20β-dihydroxy-pregna-12-one (152) gave no dimethoxy derivative with methanol and concentrated sulphuric acid.

Caglioti and Rosini[106] prepared the methyl enol ether of cholestan-3-one (23) by bromination α-to the carbonyl followed by tosyl hydrazone formation at C-3 (199). 1,4-Elimination of hydrogen bromide then led them to the Δ^{2}-olefin (200) which was converted to the methyl enol ether in 60% yield by reaction with methanol. Scheme 60 . Tosyl



Scheme 59

hydrazone formation from hecogenin acetate itself goes smoothly, the product crystallising out on leaving the reaction mixture to stand at room temperature overnight.[107] No such tosyl hydrazone formation takes place however with the β-brominated derivative (196), the infra-red

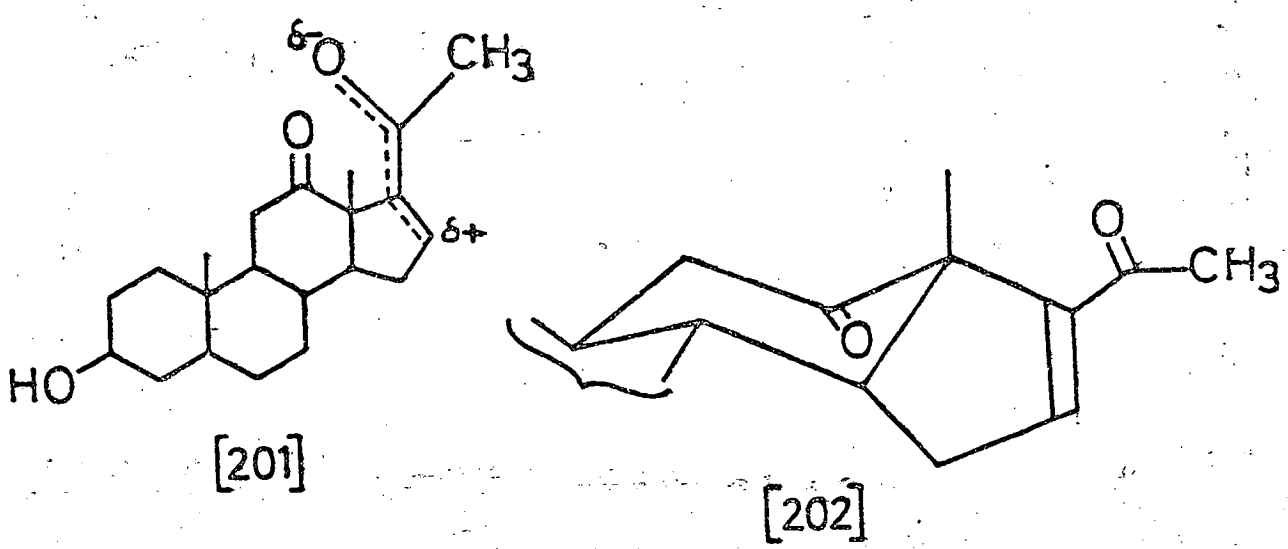


Scheme 60

spectrum of the product being idential to starting material showing a strong carbonyl absorption. The n.m.r. and mass spectra confirmed the total absence of reaction.

Enamine formation from hecogenin and pyrrolidine with titanium tetrachloride catalyst[108] also proved fruitless, the spectra of both product and starting material being virtually identical.

Carbene addition reactions can therefore form a successful route to homosteroids, but the route is limited severly by the availability of suitable substrates. The formation of $\Delta^{11(12)}$ enol ethers or esters depends critically on substituents at C-17 or at C-20 since once the C-20 hydroxyl was formed (152), enol acetylation took place albeit in only ~ 50% yield. C-20 Ketones stop this type of reaction by interaction with the 12-carbonyl, these interactions having been wellstudied by various groups[90,91,92,109] in the course of their examination of the reactions of the C-20 carbonyl. Interference between carbonyl groups was shown to be particularly strong for the Δ^{16}-12,20-dione (179) in which the $\Delta^{16(17)}$ bond and C-20 carbonyl are coplanar allowing maximum overlap necessary for the formation of the resonance hybrid (201) in the preferred S-trans conformation[92](202). Scheme 61.



[201] [202]

Scheme 61

3.2 Experimental Section

A Preparation of A-Homocholestan-4-one

3.2.i 3,3-Dimethoxy-5α-cholestane[77] (21)

To a solution of cholestan-3-one (3.5g) in methanol (1l) was added a trace of concentrated hydrochloric acid and after 1 hour, solid sodium bicarbonate (10g) which had been dried for 1 hour at 110°C. After shaking, the mixture was filtered and evaporated to dryness leaving a gum which was crystallised from ether to give 3,3-dimethoxycholestane (3.01g, 86%); m.p. 82-83° (lit.,[77] 83.5-84°); ν_{max} 1115, 1065cm^{-1}; n.m.r. (60MHz) τ 9.35 (C-18 methyl), 9.21 (C-19 methyl), 9.20 (C-26 and C-27 methyls), 9.10 (C-21 methyl), 6.87 (C-3α methoxy) 6.82 (C-3β methoxy).

3.2.ii 3-Methoxy-cholest-2-ene[78] (23)

3,3-Dimethoxy cholestane (3.0g) was dissolved in xylene (100ml) and heated for 4 hours at 220°C under nitrogen in a Carius tube. The xylene was then distilled off leaving a gum which was chromatographed on alumina (150g). Elution with benzene gave crystalline 3-methoxy cholest-2-ene (2.2g, 79%); m.p. 95-96° (lit.,[78] 95-97); ν_{max} 1675, 1208cm^{-1}; n.m.r. (60MHz) τ 9.34 (C-18 methyl), 9.25 (C-19 methyl), 9.20, 9.10, 6.45 (C-3 methoxy), 5.55 (m, $W_{\frac{1}{2}}$ = 5Hz, C-2 olefinic proton).

3.2.iii 2α,3α-Dichloromethylene-3β-methoxy-cholestane[15] (24)

3-Methoxy cholest-2-ene (2.0g) was dissolved in cyclohexane (55ml) and dry potassium tertiary butylate[110] (4.0g) added at 0°C. To this stirred mixture, chloroform (4.0g) was added dropwise. The solution turned deep red, and after stirring at room temperature for a further 30 minutes, was poured into water and extracted with ether. The ethereal solution was washed with water, dilute hydrochloric acid, saturated sodium bicarbonate and saturated salt solution, dried over magnesium sulphate and evaporated to dryness. The residue

was chromatographed on alumina (150g) and elution with benzene gave a white crystalline solid, 2α,3α-dichloromethylene-3β-methoxy-chomestane (1.5g,63%); ν_{max} 1115cm^{-1}; n.m.r. (60 MHz)τ 9.34 (C-18 methyl), 9.20, 9.18 (C-19 methyl), 9.10, 6.55 (C-3 methoxy).

3.2.iv 3-Chloro-A-homocholest-2-en-4-one[15](26)

2α,3α-Dichloromethylene-3β-methoxy-cholestane (1.5g) was dissolved in acetic acid (60ml) and water (8ml). Silver acetate (0.75g) was added and the mixture was heated under reflux for 40 hours. This was then diluted with water and extracted three times with ether. The combined ethereal layers were then washed with water,dilute hydrochloric acid, saturated sodium bicarbonate then saturated salt solution, dried over magnesium sulphate, filtered and evaporated to dryness. Chromatography of the residue on silica gel (100g) and elution with petrol-ether (40-60°) gave 3-chloro-A-homocholest-2-en-4-one as a white crystalline solid (0.5g. 37%); m.p. 100-104° (lit.,[15] 103-104°C); ν_{max} 1690, 688cm^{-1}; n.m.r. (100MHz)τ 9.338 (C-18 methyl), 9.169 (C-26 and C-27 methyls), 9.120 (C-20 methyl), 9.108 (C-19, C-26 and C-27 methyls), 9.067 (C-20 methyl) 3.29 (m, $W_{\frac{1}{2}}$ = 6Hz, C-2 olefinic proton).

3.2.v A-Homocholestan-4-one[15] (13)

3-Chloro-A-homocholest-2-en-4-one (0.15g) was dissolved in benzene (10ml) and hydrogenated in the presence of 10% palladium/charcoal catalyst (0.05g) and sodium carbonate (0.2g) at room temperature and pressure for 24 hours. After filtration, the solvent was evaporated off and the residue was recrystallised from methanol giving A-Homocholestan-4-one (0.1g, 66%); m.p. 92-95° (lit.,[15] 96-98°); ν_{max} 1700cm^{-1}; n.m.r. (100MHz)τ 9.346 (C-18 methyl), 9.201 (C-19 methyl), 9.171 (C-26 and C-27 methyls), 9.130 (C-20 methyl), 9.106 (C-26 and C-27 methyls), 9.074 (C-20 methyl).

B Preparation of 17β-methoxy-A-homoandrostan-4-one

3.2.vi 17β-Methoxy androstan-3-one[84] (166) Purdie methylation

A mixture of 17β-hydroxy-androstan-3-one (6.6g) silver oxide (12.0g)

and methyl iodide (50ml) was stirred vigorously then heated under reflux for 18 hours with continued stirring. The mixture was then diluted with water and extracted with ether. The ethereal solution was dried over magnesium sulphate, filtered and evaporated to dryness which gave a pale brown solid. Recrystallisation from petrol-ether (60-80°) gave pure 17β-methoxy-androstan-3-one (2.4g, 36%); m.p. 108-110°; ν_{max} 1718, 1120cm^{-1}; n.m.r. (60 MHz) τ 9.23 (C-18 methyl), 8.98 (C-19 methyl), 6.66 (C-17β methoxy).

3.2.vii 3,3-17β-Trimethoxy-androstane (167)

17β-Methoxy-androstan-3-one (3.5g) was dissolved in methanol and the solution was made up to 1 litre. A trace of concentrated hydrochloric acid was added, then, after 30 minutes, sodium bicarbonate (10g) which had been dried for one hour at 110°C was also added. After shaking, the solution was filtered and evaporated to dryness leaving a white solid cake of crude 3,3,17β-trimethoxy-androstane (3.6g, 90%); ν_{max} 1118, 1065cm^{-1}; n.m.r. (60MHz) τ 9.25 (C-18 methyl), 9.20 (C-19 methyl), 6.86 (C-3α methoxy), 6.82 (C-3β methoxy), 6.66 (C-17β methoxy); mass spectrum, M$^+$, $^m/_e$ 350, calculated for $C_{22}H_{38}O_3$ 350.282079 found 350.281400, error less than 2p.p.m.

3.2.viii 3,17β-Dimethoxy-androst-2-ene (168)

3,3,17β-Trimethoxy-androstane (3.0g) was dissolved in xylene (100ml) and heated under nitrogen in a Carius tube for 4 hours at 220°C. The xylene was then distilled off and the residue chromatographed on alumina (200g). Elution with benzene gave 3,17β-dimethoxy-androst-2-ene (1.7g, 63%); m.p. 68-72°; ν_{max} 1675, 1218, 1123cm^{-1}; n.m.r. (60MHz) τ 9.25 (C-18 and C-19 methyls), 6.66 (C-17β methoxy), 6.53 (C-3 methoxy), 5.5 (m, $W_{\frac{1}{2}}$= 5Hz, C-3 olefinic proton); mass spectrum, M$^+$, $^m/_e$ 318, calculated for $C_{21}H_{34}O_2$ 318.255866 found 318.254709 error less than 4 p.p.m.

3.2.ix 2α3α-Dichloromethylene-3β, 17β-dimethoxy-androstane (169)

3,17β-Dimethoxy-androst-2-ene (1.6g) was dissolved in cyclohexane (55ml) and dry potassium tertiary butylate (4g) was added at 0°C. To this stirred mixture, chloroform (4g) was added dropwise. After complete addition, the mixture was stirred for 30 minutes at room temperature then diluted with water and extracted with ether. The ethereal solution was washed with water, dilute hydrochloric acid, saturated sodium bicarbonate and finally a saturated salt solution dried over magnesium sulphate, filtered and evaporated to dryness to leave a yellow solid. This was chromatographed on alumina (100g). Elution with benzene gave crystalline 2α,3α-dichlormethylene-3β,17β-dimethoxy-androstane (1.5g, 75%); m.p. 120-122°; ν_{max} 1120, 1110, 685cm^{-1}; n.m.r. (60MHz) τ 9.25 (C-18 methyl), 9.21 (C-19 methyl), 6.66 (C-17β-methoxy), 6.55 (C-3β methoxy); mass spectrum, M$^+$, $^m/_e$ 404, 402, 400, calculated for $C_{22}H_{34}O_2\ ^{35}Cl_2$ 400.187672, found 400.189674, error less than 5 p.p.m., calculated for $C_{22}H_{34}O_2\ ^{35}Cl^{37}Cl$ 402.190622 found 402.189769 error less than 3 p.p.m., calculated for $C_{22}H_{34}O_2\ ^{37}Cl_2$ 404.187672 found 404.187889 error less than 1 p.p.m.

3.2.x 3-Chloro-17β-methoxy-A-Homoandrost-2-en-4-one (170)

2α,3α-Dichloromethylene-3β,17β-dimethoxy-androstane (1.5g) was dissolved in acetic acid (72ml) and water (10ml). Silver acetate (0.9g) was added and the reaction mixture heated under reflux for 40 hours. The mixture turned deep red. After dilution with water, the steroid was extracted with ether, the ethereal solution was washed with water, dilute hydrochloric acid, saturated sodium bicarbonate and saturated salt solution, dried over magnesium sulphate, filtered and evaporated to dryness. The brown residue was chromatographed on alumina (100g). Elution with benzene gave a yellow crystalline solid. One recrystallisation from ethanol gave pale yellow needles of 3-chloro-17β-methoxy-A-Homoandrost-2-en-4-one (0.59g,45%); m.p. 65-70°; ν_{max} 1690, 1120cm^{-1}.

3.2.xi 17β-Methoxy-A-homoandrost-4-one (171)

3-Chloro-17β-methoxy-A-homoandrost-2-en-4-one (0.5g) was dissolved in benzene (20ml) and hydrogenated for 24 hours at room temperature and pressure in the presence of 10% palladium/charcoal catalyst (75mg) and sodium carbonate (0.3g). The mixture was filtered and the benzene was evaporated leaving a colourless gum which on recrystallisation from methanol gave 17β-methoxy-A-homoandrostan-4-one (0.3g 67%); m.p. 94-96°; ν_{max} 1702, 1120cm^{-1}; n.m.r. (100 MHz) τ 9.25 (C-18 methyl), 9.20 (C-19 methyl), 6.66 (C-17β-methoxy); mass spectrum, M^+, $^m/_e$ 318 (100%), $^m/_e$ 304 (25%), $^m/_e$ 286 (12%), $^m/_e$ 246 (30%); calculated for $C_{21}H_{34}O_2$ 318.255866 found 318.255022 error less than 3 p.p.m.

C Preparation of 17β-acetoxy-A-homoandrostan-4-one

3.2.xii 3,17β-Diacetoxy-androst-3-ene[86] (68)

Androstanolone (10g) was stirred in carbon tetrachloride (95ml) during the dropwise addition of 72% perchloric acid (0.2ml) in acetic anhydride (10ml). The mixture was then allowed to stir at room temperature for a further 1.5 hours. After this time the mixture was transferred to a separating funnel and washed with ice-cold 5% sodium hydroxide then with water. The organic layer was dried over magnesium sulphate, filtered and evaporated to dryness giving 3,17β-diacetoxy androst-2-ene as a white solid (10.9g,85%) giving one spot on t.l.c. m.p. 164-169° (lit.,[86] 172-174); ν_{max} 1750, 1730, 1250, 1223cm^{-1}; n.m.r. (60MHz) τ 9.21 (C-18 methyl), 9.17 (C-19 methyl), 7.96 (C-17β acetoxy), 7.90 (C-3 acetoxy), 5.37 ('t', J=8Hz,C-17α proton), 4.74 (m,$W_{\frac{1}{2}}$=4Hz, C-2 olefinic proton).

3.2.xiii Phenyl (bromodichloromethyl) mercury[27d]

To a dry litre flask equipped with a nitrogen inlet and Teflon stirring paddle was introduced phenyl mercuric chloride (50.0g). The material remaining in the weighing beaker was rinsed into the flask with

dry tetrahydrofuran (200ml). To this was added bromodichloromethane (40.0g) followed by tetrahydrofuran (100ml) rinse. This mixture was stirred and maintained at -25°C during the entire reaction time by external cooling. The contents of a bottle of commercial potassium tertiary butylate (25g) were quickly transferred under nitrogen to a dry 500ml flask containing dry tetrahydrofuran (150ml) and the mixture stirred under nitrogen until the base had completely dissolved. To this solution was added tertiary butanol (16.5g, distilled from sodium and stored under dry nitrogen) in tetrahydrofuran (50ml) over a 10 minute period by means of a pressure equalising dropping funnel. The resulting yellowish suspension was cooled to room temperature and transferred to a dropping funnel. This potassium tertiary butylate-tertiary butanol suspension was then added to the cooled phenyl mercuric chloride-haloform-tetrahydrofuran solution over a 15-20 minute period. Upon completion of addition, the reaction mixture was stirred for 5 minutes at -25°C then transferred to a 2 litre flask. The solvent was stripped off rapidly at reduced pressure using a rotary evaporator and a -78° trap. Final traces of solvent were removed by warming on a water bath below 25°. Reagent grade benzene (800ml) was then added to the dry residue and the mixture was shaken until the solid had partially dissolved. Subsequently, distilled water (100ml) was added and the mixture was shaken thoroughly. The benzene layer was then carefully decanted through a filter into a 2 litre flask, the aqueous layer being washed with more benzene (200ml). The benzene extract and washings were evaporated to dryness and the residue was quickly dissolved in hot hexane:chloroform (3:1). After a hot filtration, the hexane:chloroform solution was immediately chilled to 0°C. The product which crystallised out was filtered off and stored at -15°. The mother liquors were evaporated to dryness and the residue was recrystallised from hexane-chloroform (3:1) which gave a second crop of colourless needles of phenyl (bromodichlormethyl) mercury which was added to the first crop

(26g,37%) m.p. 108-110°C (dec) (lit.,[27d] 110-111° dec).

3.2.xiv 3β,17β-Diacetoxy-2α,3α-dichloromethylene-androstane (172)

3β,17β-Diacetoxy-androst-2-ene (2.5g) was dissolved in dry benzene (50ml) and phenyl (bromodichloromethyl) mercury (10g) added and the mixture was heated under reflux. The n.m.r. spectrum of an aliquot of the reaction mixture after 4 hours showed the carbene addition to have gone 64% to completion shown by the partial disappearance of the C-2 olefinic proton multiplet at τ4.74. Complete reaction occurred after 12 hours when the micture was filtered to remove phenyl mercuric bromide formed in the reaction, and the solution was evaporated to dryness. The residual brown gum was taken up in a little dry chloroform, filtered and again evaporated to dryness. One crystallisation from methanol then yielded pure 3β,17β,diacetoxy-2α-3α-dichlormethylene-androstane (1.8g,59%), m.p. 171-179° t.l.c. showed the product as one red spot having the same polarity as starting material (yellow spot); νmax 2960, 1740, 1250, 1225, 685cm^{-1}; n.m.r. (60MHz) τ 9.22 (C-18 methyl), 9.18 (C-19 methyl), 7.98 (C-17β acetoxy), 7.93 (C-3β acetoxy), 5.42 (t, J-8Hz, C-17α proton).

3.2.xv 3-Chloro-17β-hydroxy-A-homoandrost-2-en-4-one (173)

3β,17β-Diacetoxy-2α,3α-dichlormethylene-androstane (200mg) was dissolved in pyridine (5ml) and potassium hydroxide (25mg) in ethanol (10ml) was added and the solution was stirred for 18 hours at room temperature. The mixture turned orange almost immediately. Ether was then added and the mixture was washed with dilute hydrochloric acid which removed the colour. The organic layer was then dried over magnesium sulphate, filtered and evaporated to dryness which left a pale yellow oil (123mg) t.l.c. of which showed one main spot less polar than starting material, and a minor spot which corresponded to starting material; ν_{max} 1730, 1650, 1178, 903, 728cm^{-1};

n.m.r. (60MHz)τ 9.24 (C-18 methyl), 8.96 (C-19 methyl), 4.30 (m, $W_{\frac{1}{2}}$ = 8Hz, C-2 olefinic proton).

3.2.xvi 17β-Acetoxy-A-homoandrostan-4-one (28)

The crude 3-chloro-17β-hydroxy-A-homoandrost-2-enol-4-one (100mg) was dissolved in benzene and hydrogenated at room temperature and pressure overnight in the presence of 10% palladium/charcoal (50mg) catalyst and sodium carbonate (400mg). The solution was then filtered and evaporated to dryness, the residual gum was taken up in acetic acid (5ml) and pyridine (2ml) in acetic anhydride (2ml) was added. After standing overnight, water was added and the steroid was extracted into ether, the organic layer washed with water followed by 5% sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness. One crystallisation from n-hexane gave 17β-acetoxy-A-homoandrostan-4-one as a white solid (71mg, 78%); m.p. 148-150°; ν_{max} 1730, 1255cm^{-1}; mass spectrum, $^{m}/_{e}$ 346 (M^{+}, 67%), $^{m}/_{e}$ 290 (100%), $^{m}/_{e}$ 272 (40%), 231 (65%).

D Preparation of 3β,20β-dihydroxy-C-homopregn-12a-one

3.2.xvii Attempted Enol acetylation of hecogenin acetate

a. With perchloric acid catalyst

Hecogenin acetate (5g) was dissolved in carbon tetrachloride (50ml) and acetic anhydride (5ml) and perchloric acid (0.2ml) added with stirring at room temperature. After 1.5 hours, water was added, the precipitate was filtered off and dried *in vacuo* leaving a white solid (4.7g). T.L.C. showed two spots, one of which corresponded to starting material, the second to a slightly more polar compound, ν_{max} 1730, 1703, 1245cm^{-1}; n.m.r. (60MHz)τ 9.05 (C-18 methyl), 8.95 (C-19 methyl), 8.02 (C-3β acetoxy), hecogenin acetate; and ν_{max} 1730, 1365, 1245cm^{-1}; n.m.r. (60MHz)τ 9.05, 7.85 (C-23 acetyl), 23Ξ- acetyl-hecogenin acetate.

b.With toluene-4-sulphonic acid catalyst

Hecogenin acetate (5g) was dissolved in warm acetic anhydride (285ml) and toluene-4-sulphonic acid (5g) added. The acetic ahydride was then slowly distilled off through a short Vigreux column until about one third of the original volume remained. The rest of the acetic anhydride was then removed in vacuo and the residue was taken up in ether. The ether solution was washed with ice-cold 5% sodium hydroxide then water, before being dried over magnesium sulphate, filtered and evaporated to dryness leaving a pale yellow solid (4.7g) which showed no reduction of intensity of the carbonyl peak due to the C-12 ketone in the infra-red spectrum. The solid was then treated with 10% ethanolic potassium hydroxide for 30 minutes under reflux. The ethanol was then stripped off and water was added. The precipitated steroid was filtered off and dried in vacuo as a white solid (4.1g), ν_{max} 3580, 1703, 1360, 1010, 955, 935, 900cm^{-1}; 23ξ- acetyl-hecogenin.

3.2.xviii ψ-Hecogenin[87]

Hecogenin acetate (10g) was dissolved in n-octanoic acid (200ml) and acetic anhydride (5ml) was added. The low boiling solvents were distilled off until the temperature reached 240°C, the boiling point of n-octanoic acid. The reaction mixture was then heated under reflux for 2 hours. Ether (500ml) was added to the cooled solution and the mixture washed in 2N sodium hydroxide and water. The ethereal solution was then dried over magnesium sulphate, filtered and evaporated to dryness to leave a dark red gum. This residue was heated under reflux for 30 minutes in 5% methanolic potassium hydroxide then addition of hot water precipitated a white solid which was filtered off and washed with water containing a trace of pyridine to give pure ψ-hecogenin (8.2g, 90%); m.p. 185-189° (lit.,[87], 190-191°); ν_{max} 3450, 1702, 1388cm^{-1}; n.m.r. (100 MHz) τ 9.12 (C-18 methyl), 8.80 (C-19 methyl); mass spectrum, M$^+$, $^m/_e$ 430 (71%).

3.2.xix Enol acetylation of ψ-hecogenin

a. with perchloric acid catalyst

ψ-Hecogenin (5g) was reacted by the procedure described in 3.2.xviii.a. The product was a yellow gum (4.3g), ν_{max} 3450, 1735, 1702, 1388, 1240cm^{-1}; t.l.c. showed one spot, 3β,26-diacetoxy-ψ-hecogenin.

b. with toluene-4-sulphonic acid catalyst

ψ-Hecogenin (2g) was reacted by the procedure described in 3.2.xviiib. The product was a yellow gum (1.2g). The infra-red spectrum and t.l.c. again indicated that the sole product was 3β-26-diacetoxy-ψ-hecogenin.

3.2.xx 3β-26-Diacetoxy-ψ-hecogenin[87] (176)

ψ-Hecogenin (5g) was dissolved in glacial acetic acid (50ml) and acetic anhydride (15ml). The solution was cooled to 18°C and perchloric acid (0.8ml) in acetic acid was added, the temperature being maintained below 35°C. After 30 minutes at room temperature, ice and water were added and the resulting precipitate extracted into ether. The ether extracts were washed with 5% sodium hydroxide solution and water, dried over magnesium sulphate, filtered and evaporated to dryness to give the crude solid product which after one crystallisation from ethanol afforded pure 3β-26-diacetoxy-ψ-hecogenin (5.24g, 87%); m.p. 91-94° (lit.,[87] 92.5 - 94°); ν_{max} 3450, 1730, 1702, 1240cm^{-1}; n.m.r. (100 MHz) τ 9.11 (C-18 methyl), 8.79 (C-19 methyl), 8.01 (C-3β and C-27 acetoxy groups).

3.2.xxi 3β-Acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnane-12,20-dione[87] (177)

3β-26-Diacetoxy-ψ-hecogenin (8.5g) was dissolved in glacial acetic acid (60ml) and 1.39N chromium trioxide in 90% acetic acid (62ml; 30% excess) was added slowly, the temperature was maintained below 30° for 3 hours. Excess oxidant was destroyed by the addition of methanol, the steroid precipitated by the addition of water and extracted with ether. The

combined ether extracts were washed with 5% sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to dryness to leave a pale green glass. Attempted crystallisation from ethanol left 3β-acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnane-12,20-dione still as a glass (7.8g, 87%), ν_{max} 2960, 1730, 1705, 1245, 1040cm^{-1}; n.m.r. (100MHz) τ 9.08 (C-methyl), 9.06 (C-26 methyl), 8.63 (C-19 methyl), 8.00 (C-3 acetoxy), 7.96 (C-27 acetoxy), 7.83 (C-21 methyl); mass spectrum, M*, $^{m}/_{e}$ 546 (21%).

3.2.xxii 3β-Acetoxy-5α-pregn-16-ene-12, 20-dione (178)

3β-Acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnane-12,20-dione (5g) was dissolved in benzene (50ml) and petroleum ether (40-60°, 150ml). Spence grade 'H' alumina (50g) was added and the slurry was stirred at room temperature for 2 hours. The alumina was then filtered off and washed with 1:1 ether:methylene chloride (500ml). Evaporation of the combined filtrate and eluate and recrystallisation of the residue from ether gave 3β-acetoxy-5α-pregn-16-ene-12,20-dione (3.1g, 91%) as a white solid, m.p. 179-180° (lit.,[87] 178-180°); ν_{max} 2950, 1730, 1715, 1678, 1242, 1040cm^{-1}, n.m.r. (100 MHz) τ 9.05 (C-methyl), 8.69 (C-19 methyl), 8.00 (C-3β acetoxy), 7.70 (C-21 methyl), 3.42 (m, $W_{\frac{1}{2}}$ = 2Hz, C-16 olefinic proton).

3.2.xxiii Enol acetylation of 3β-acetoxy-5α-pregn-16-ene-12,20-dione[90]

3β-Acetoxy-5α-pregn-16-ene-12,20-dione (250mg) was dissolved in acetic anhydride (15ml) and toluene-4-sulphonic acid (250mg) added. The acetic anhydride was slowly distilled through a short Vigreux column till about one third of the original volume remained. The solution darkened considerably and after distillation was complete, the residue was taken up in ether and the ethereal solution washed with ice-cold 5% potassium hydroxide solution then with water, dried over magnesium sulphate, filtered and evaporated to dryness to leave a dark red glass (298 mg), t.l.c.

of which showed two spots, one corresponding to starting material and a second of lower polarity; ν_{max} 1730, 1710, 1680, 1245cm^{-1}; n.m.r. (100 MHz) τ 9.05 (C-18 methyl), 8.69 (C-19 methyl), 8.00 (C-3 acetoxy), 7.70 (C-21 methyl), 3β-acetoxy-5α-pregn-16-ene-12,20-dione; ν_{max} 1730, 1710, 1663, 1245, 1210cm^{-1}; n.m.r. (100 MHz) τ 9.05 (C-18 methyl), 8.74 (C-19 methyl), 8.00 (C-3β acetoxy and C-16 acetoxy), 7.93 (C-20 enol acetate), 3β, 16,20-triacetoxy-5α-pregn-17-en-12-one. (Ca 50%).

3.2.xxiv 3β-Acetoxy-5α-pregnane-12,20-dione (179)

3β-Acetoxy-5α-pregn-16-ene-12,20-dione(3g) was dissolved in ethyl acetate (50ml) and hydrogenated for 2 hours at room temperature and pressure in the presence of 10% palladium/charcoal catalyst (250mg). After filtration, the solution was evaporated to dryness and the residue was crystallised from ethyl acetate giving pure 3β-acetoxy-5α-pregnane-12, 20-dione (3.0g, 100%); m.p. 186-187° (lit.,[87] 188-190°); ν_{max} 2910, 1738, 1710, 1250, 1030cm^{-1}; n.m.r. (60 MHz) τ 9.07 (C-18 methyl), 9.05 (C-19 methyl), 7.98 (C-3β-acetoxy), 7.75 (C-21 methyl).

3.2.xxv Enol acetylation of 3β-acetoxy-pregnane-12,20-dione

a.With perchloric acid catalyst

3β Acetoxy pregnane-12,20-dione (250mg) was reacted as above 3.2.xviiia. The t.l.c, infra-red and n.m.r. spectra of the product (223mg), a brown glass, were identical to those of the starting material.

b.with toluene-4-sulphonic acid catalyst

3β-Acetoxy-pregnane-12,20-dione (250mg) was reacted as above 3.2.xviiib. The t.l.c. of the product, a red solid (253mg) showed one main spot and one minor spot of higher polarity, n.m.r. (60MHz) τ 7.98 (C-3β acetoxy), 7.90 (C-20 enol acetate), C-17 proton triplet now gone; mass spectrum, $^{m}/_{e}$ 416 (M^{+} 10%), $^{m}/_{e}$ 374 (100%), 3β,20-diacetoxy-pregn-17-en-12-one.

3.2.xxvi 3β-Acetoxy-12-ethylenedioxy-pregnan-20-one[94] (180)

3β-Acetoxy-pregnane-12-20-dione (3g) in absolute methylene chloride (15ml) was stored at room temperature for 72 hours with ethylene glycol (25ml) and boron trifluoride etherate (5.5ml). Large quantities of water and methylene chloride were then added and the steroid was taken up in the organic layer which was washed with sodium bicarbonate and water, dried over magnesium sulphate and evaporated to dryness. Recrystallisation of the residue from ether gave 3β-acetoxy-12-ethylenedioxy-pregn-20-one (2.75g, 81%); m.p. 154-156° (lit.,[94] 158-160°); ν_{max} 2910, 1718, 1700, 1260, 1030cm^{-1}; n.m.r. (60MHz) τ 9.16 (C-18 and C-19 methyls), 7.98 (C-3β acetoxy), 7.86 (C-21 methyl), 6.08, 5.98 (4 protons of ketal); mass spectrum, M^+, $^m/_e$ 418 (100%).

3.2.xxvii 3β,20β-Dihydroxy-12-ethylenedioxy-pregnane[95] (181)

3β-Acetoxy-12-ethylenedioxy-pregnan-20-one (3g) and sodium hydroxide (1.5g) were dissolved in methanol (300ml) and sodium borohydride (0.6g) in 50% aqueous methanol (60ml) was added. The reaction mixture was stored at room temperature for 60 hours then diluted with water and extracted with ether. The ether layer was washed with 5% sodium bicarbonate and water, dried over magnesium sulphate, filtered and evaporated to dryness. Recrystallisation from methanol:ether (1:1) gave 3β, 20β-dihydroxy-12-ethylene-dioxy-pregnane (2.9g, 97%); m.p. 196-201°. (lit.,[95] 198-200°); ν_{max} 3485, 2900, 1050cm^{-1}; mass spectrum, M^+, $^m/_e$ 378 (100%).

3.2.xxviii 3β,20β-Dihydroxy-pregn-12-one[99] (152)

3β,20β-Dihydroxy-12-ethylenedioxy-pregnane (2.0g) was dissolved in 90% acetic acid and was heated on a steam bath for one hour. The mixture was then poured into water and the steroid was extracted into ether. The combined ether extracts were washed with 10% sodium bicarbonate and water, dried over magnesium sulphate, filtered and evaporated to dryness. Crystallisation from methylene chloride-acetone gave 3β,20β-dihydroxy

pregn-12-one (1.4g., 77%); m.p. 231-233° (lit.,[99] 231-233°); ν_{max} 3450, 2890, 1698cm^{-1}; n.m.r. (60MHz) τ 9.13 (C-18 methyl), 8.92 (C-19 and C-21 methyls); mass spectrum, M^+, $^m/_e$ 334 (17%), $^m/_e$ 319 (22%), 290 (71%), 275 (21%), 249 (100%).

3.2.xxix 3β, 12,20β-Triacetoxy-pregn-11-ene (186)

3β,20β-Dihydroxy-pregn-12-one (o.2g) was dissolved in acetic anhydride (20ml) and toluene-4-sulphonic acid (0.2g) was added. The acetic anhydride was slowly distilled off over a period of approximately 1 hour through a short unpacked column until only 2-3ml remained. The residue was taken up in ether and the extract washed with 10% sodium bicarbonate and water, dried over magnesium sulphate; filtered and evaporated to dryness to leave a red glass (0.25g); ν_{max} 1715, 1255cm^{-1}; n.m.r. (60MHz) τ 9.08 (C-18 methyl), 8.98 (C-19 methyl), 8.80 (C-21 methyl), 8.02 (C-20β acetoxy), 7.98 (C-3β acetoxy), 3β,20β-diacetoxy-pregn-12-one(187); 7.90 (C-12 enol acetate), 4.78 ($m, W_{\frac{1}{2}}$ = 3Hz, C-11 olefinic proton), 3β,12,20β-triacetoxy-pregn-11-ene (186); mass spectrum, M^+, $^m/_e$ 418 (39%), 3β,20β-diacetoxy pregn-12-one (187); M^+, $^m/_e$ 460 (8%), 3β,12,20β-triacetoxy-pregn-11-ene (186).

3.2.xxx Attempted enol acetylation of 3β, 20β-dihydroxy-pregn-12-one with perchloric acid catalyst

3β,20β-Dihydroxy-pregn-12-one (110mg) was reacted as described above 3.2.xviiia except the reaction time was 2 hours. The t.l.c., infra-red and n.m.r. spectra of the product, a brown glass, were consistent with those for 3β,20β-diacetoxy-pregn-12-one, showing no trace of the enol acetate.

3.2.xxxi 11α,12α-Dichloromethylene-3β,12β,20β-triacetoxy-pregnane (188)

The crude 3β,12,20β-triacetoxy-pregn-11-ene (250mg) was dissolved in dry benzene and phenyl (bromodichloromethyl) mercury (1g)

added and the reaction mixture was heated under reflux for 48 hours then stirred at room temperature for 4 days. The phenyl mercuric bromide formed in the reaction was filtered off and the solution was evaporated to dryness. The brown solid residue was then taken up in dry chloroform and filtered to remove final traces of the phenyl mercuric bromide. Evaporation to dryness gave a brown solid (176mg) ν_{max} 1730, 1715, 1240, 1215, 720cm^{-1}; n.m.r. (60MHz) τ 9.10 (C-18 methyl), 9.00 (C-19 methyl), 8.40 (C-21 methyl), 8.03 (C-20β acetoxy), 8.00 (C-3β acetoxy), 7.96 (C-12β acetoxy). The olefinic proton doublet (τ4.78) found in the original enol acetate was no longer present.

3.2.xxxii 12-Chloro-3β,20β-dihydroxy-C-homopregn-11-en-12a-one(189)

11α,12α-Dichloromethylene-3β,12β,20β-triacetoxy-pregnane (130mg) was dissolved in pyridine (5ml) and potassium hydroxide (60mg) in ethanol (10ml) was added. The mixture was then stirred at room temperature for 72 hours. Ether was then added and the solution was washed with dilute hydrochloric acid then water, dried over magnesium sulphate, filtered and evaporated to dryness to leave a brown solid (64mg, 74%). The t.l.c showed one main spot with two minor spots and one trace impurity; ν_{max} 3600, 3450, 2920, 1695cm^{-1}; 12-chloro-3β,20β-dihydroxy-C-homopregn-11-en-12a-one; ν_{max} 1710 (shoulder)cm^{-1}, 3β,20β-dihydroxy-pregn-12-one; n.m.r. (60MHz) τ 9.12 (C-18 methyl), 8.95 (C-19 methyl), 5.34 (m, $W_{\frac{1}{2}}$ = 6Hz, C-11 olefinic proton).

3.2.xxxiii 3β,20β-Dihydroxy-C-homopregn-12a-one(190)

12-Chloro-3β,20β-dihydroxy-C-homopregn-11-en-12a-one (52mg) was dissolved in benzene (10ml) and was hydrogenated at room temperature and pressure overnight in the presence of 10% palladium/charcoal catalyst (30mg). The catalyst was filtered off and the solution was evaporated to dryness. The t.l.c. of the product, a red gum (38 mg) showed only one

diffuse spot. Crystallisation from acetone gave a white solid product (18 mg) of 3β,20β-dihyroxy pregn-12-one; mass spectrum, M^+, $^m/_e$ 334 (13%). The mother liquors were evaporated to dryness (29 mg) ν_{max} 3600, 3450, 2920, 1700, 1695cm^{-1}; n.m.r. (60MHz) τ 9.10 (C-18 methyl), 8.92 (C-21 methyl), 8.90 (C-19 methyl); mass spectrum, $^m/_e$ 348 (M^+, 13%), $^m/_e$ 333 (27%), 3β,20β-dihydroxy-C-homopregn-12a-one, calculated for $C_{22}H_{36}O_3$ 348.266430 found 348.265370 on error of less than 3 p.p.m.; ν_{max} 1710cm^{-1}; mass spectrum, $^m/_e$ 334 (M^+, 27%), 319 (17%), 3β,17β-dihydroxy pregn-12-one; mass spectrum, $^m/_e$ 346 (M^+ 21%), 3β,20β-dihydroxy-C-homopregn-11-en-12a-one, calculated for $C_{22}H_{34}O_3$ 346.250781, found 346.250648, an error of less than 1 p.p.m. (191) These three components were present in approximately 6:3:1 relative abundance estimated from the spectra.

E. Attempted preparations of other suitable substrates for carbene addition leading to ring-C expansion

3.2.xxxiv 11β-Bromo-hecogenin acetate[103,104](196)

Hecogenin (10g) was dissolved in absolute ethanol (325 ml) and 8N hydrochloric acid in ethanol (8 ml) was added. Bromine (1.5 ml) was then added during 4.5 hours in a stream of dry nitrogen. After complete addition, the mixture was stirred for 1 hour at room temperature then the product was precipitated by pouring into water, filtered off and dried *in vacuo*. Two crystallisations from methanol gave 11β-bromo-hecogenin (5.3g, 46%) m.p. 150-154 (lit[103], 154-6); ν_{max} 1730, 1706, 1238cm^{-1}; n.m.r. (60 MHz) τ 9.08 (C-18 methyl), 8.95 (C-19 methyl), 7.97 (C-3β acetoxy).

3.2.xxxv $\Delta^{9(11)}$-Hecogenin[104](197)

11β-Bromo-hecogenin acetate (1.4g) was added to a stirred mixture of calcium carbonate (700 mg) in dimethylacetamide (50ml), under

reflux. After 80 minutes the mixture was cooled and the product precipitated by pouring into dilute hydrochloric acid. The solid was filtered off and dried *in vacuo*. Crystallisation from acetone gave $\Delta^{9(11)}$-hecogenin (61mg, 56%) m.p. 170-176° (lit.,[104] 174-178°); n.m.r. (60MHz) τ 9.10 (C-18 methyl), 8.95 (C-19 methyl), 4.27 (S, $W_{\frac{1}{2}}$ = 2 Hz, C-11 olefinic proton); mass spectrum, M^+, $^m/_e$ 428 (6%).

3.2.xxxvi Reaction of $\Delta^{9(11)}$-hecogenin acetate with phenyl (bromo dichloromethyl) mercury

$\Delta^{9(11)}$-Hecogenin (53 mg) was dissolved in dry benzene (4 ml) and phenyl (bromodichloromethyl) mercury (154mg) added and the mixture was heated under reflux. A precipitate formed due to decomposition of the phenylmercuric halide and after 8 hours the reaction was cooled to room temperature, filtered, and water added to precipitate the steroid which was extracted into ether. The ethereal solution was dried over magnesium sulphate, filtered and evaporated to dryness leaving a pale yellow solid (52 mg) the t.l.c., infra-red and n.m.r. spectra of which showed it to be unreacted $\Delta^{9(11)}$-hecogenin.

3.2.xxxvii Reaction of 12-ketones with methanol (Scheme 59)

Hecogenin, Ψ-hecogenin, 3β-hydroxy-pregn-16-en-12,20-dione, 3β-hydroxy-pregna-12,20-dione and 3β,20β-dihydroxy-pregn-12-one, were all reacted with methanol and concentrated hydrochloric acid as described above 3.2.i. The t.l.c's, infra-red and n.m.r. spectra of the products from all five reactions were consistent with those of starting material only showing no evidence for the corresponding dimethoxy derivatives.

3.2.xxxviii Hecogenin acetate tosyl hydrazone (107)

Hecogenin acetate (2.0g) in chloroform (15ml) was added to toluene-4-sulphonhydrazide (1.0g) in a mixture of ethanol (20ml) and concentrated hydrochloric acid (0.5ml). On standing overnight, a heavy

precipitate formed which was filtered off, washed with methanol and dried in vacuo giving hecogenin acetate tosyl hydrazone (2.48g, 91%) m.p. 278-280 (decomp) (lit.,[107] 278-280); ν_{max} 3150, 2920, 1715, 1340, 1245, 1160, 910, 825cm^{-1}; n.m.r. (60MHz) τ 9.17 (C-18 methyl), 9.13 (C-19 methyl), 8.98 (C-3β acetoxy), 7.56 (tosyl hydrazone methyl), 2.10, 2.23, 2.64, 2.78 (d,d,8Hz,8Hz 4 aromatic protons).

3.2.xxxix Reaction of 11β-bromo-hecogenin acetate with toluene-4-sulphonhydrazide

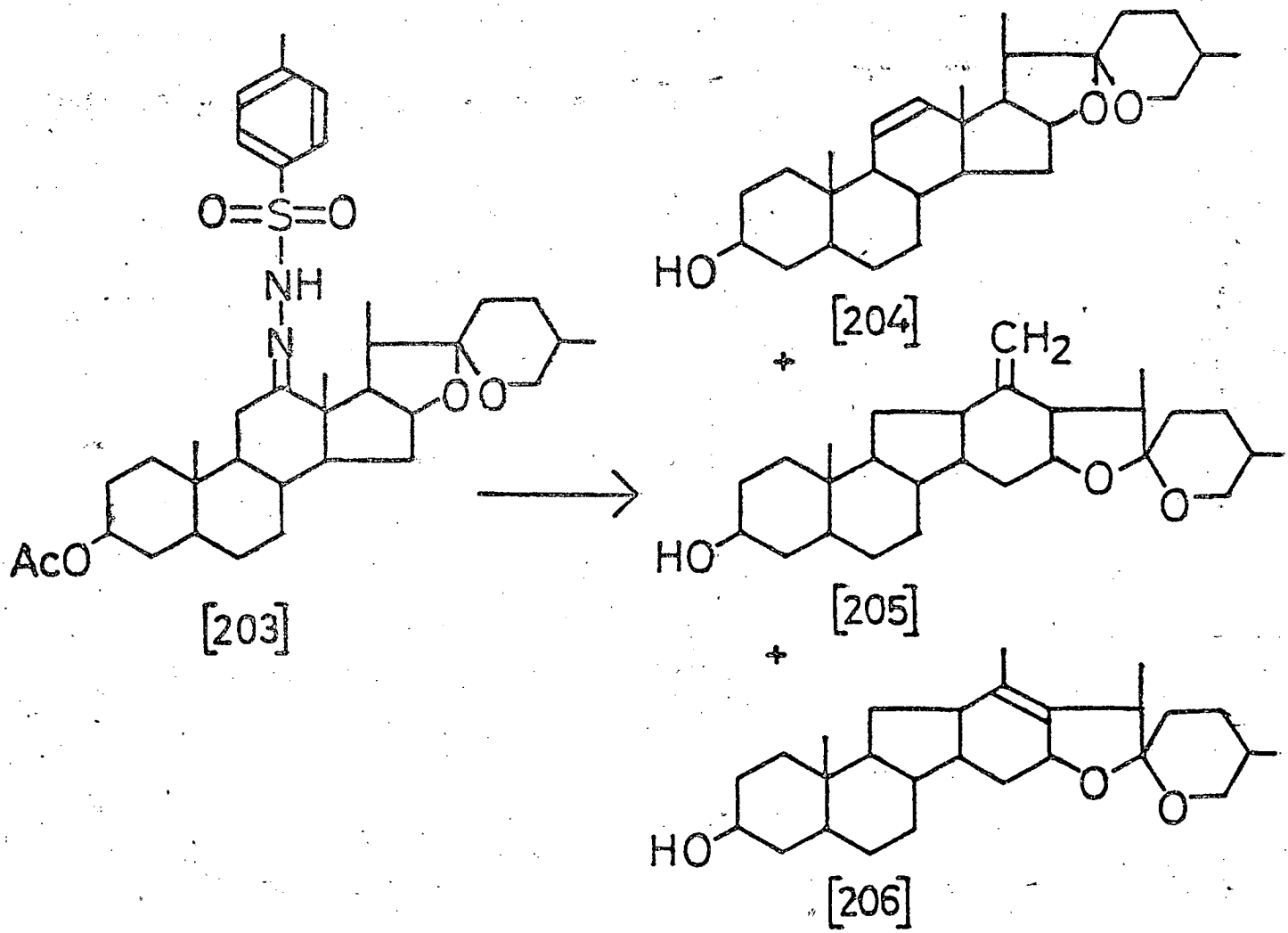
11β-Bromo-hecogenin acetate (2.2g) was reacted with toluene-4-sulphonhydrazide (1.2g) as described above 3.2.xxxviii, no precipitate formed and the t.l.c, infra-red and n.m.r. spectra of the product, precipitated by addition of water, were identical to those of 11β-bromo hecogenin acetate starting material.

3.2.xxxx Reaction of hecogenin with pyrrolidine[108]

Hecogenin (4.75g) was dissolved in dry benzene and pyrrolidine (10ml) in dry benzene (10ml) added to the stirred solution at 0-10°C under nitrogen. Titanium tetrachloride(0.3g) in dry benzene (10ml) was then added dropwise over a 40 minute period. The mixture was finally stirred at room temperature for 3 hours after which time the mixture was filtered and the solvent removed in vacuo to leave an off-white solid (4.52g), the infra-red and n.m.r. spectra of which showed no enamine formation having taken place but in fact were identical to those of hecogenin starting material.

4.1 Some other Re-arrangements leading to Ring-Expanded Steroids

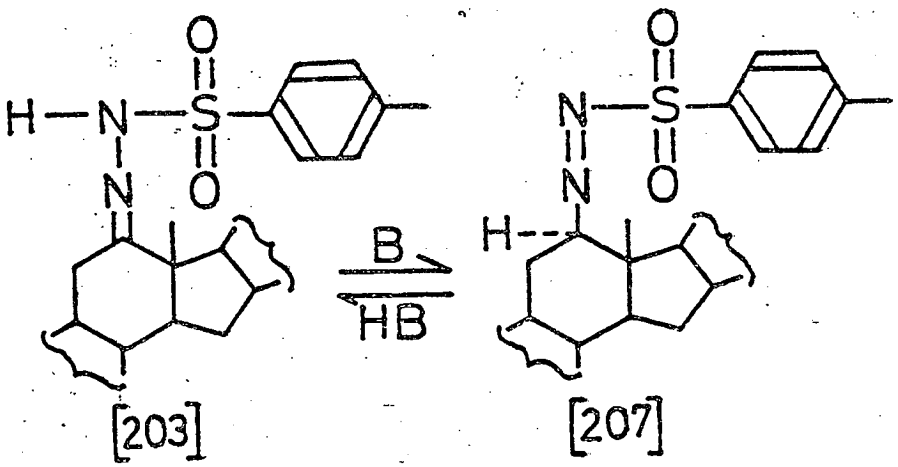
Elks et al.,[111] in 1954, in attemping the re-arrangement of the 12-toluene-4-sulphonhydrazone of hecogenin acetate with caustic alkali in diethylene glycol at 130-140°C, found three products. Scheme 62 . The required 3β-acetoxy-5α:22α-spirost-11-ene (204) for conversion to 11-oxotigogenin and so by a known route to cortisone, was formed in yields of up to 25%. The two other products (205) and (206) resulted from Wagner-Meerwein re-arrangement[112] and were formed in 50-55% and up to 5% yields respectively.



Scheme 62

It is known that Wagner-Meerwein rearrangements occur most readily or in some cases only when the four reacting centres lie in a plane. The 12-mesylate rearranges in similar fashion[113] giving comparable yields of all three products. In this case the C12-O bond is β-orientated and the conditions of coplanarity are satisfied by the chains O-C12-C13-C14 and O-C12-C11-C9. In the 12α-epimer however, there are no similar sets of coplanar centres and consequently shows no rearrangement. Analogous compounds in the bile acid series are known to undergo simple eliminations under more vigorous conditions with formation of an 11:12 double-bond, the complanar atoms in this instance being O-C12-C11-11βH[114].

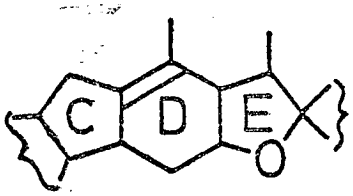
In the decomposition of the 12-toluene-4-sulphonhydrazone, a double-bond rearrangement under the influence of base was proposed Scheme 63 , and that it is the azo-form (207), which may well only exist transitorily, that undergoes decomposition and rearrangement through the conventional carbonium ion intermediates.[115,116] In such a double-bond rearrangement, the newly formed single-bond between C-12 and N will be



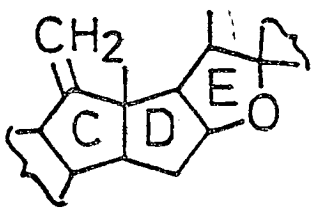
Scheme 63

predominantly in the more stable equatorial and β-configuration and the geometrical factors will be similar to those for the mesylate. Formation of some Δ^{11}-olefin during the decomposition suggests that a

proportion of the azo-intermediate was the C12-N bond in the α-configuration, suitably disposed for involvement of the 11β hydrogen atom. Because of the co-planarity of the β-bond at C-12 with both C-13 and C-14 and with atoms C-11 and C-9, various compounds might have arisen. C12-C13-C14 could have given three C-nor, D-homo products (205), (206) and (208). C12-C11-C9 could have given only an exocyclic methylene adduct (209). The second mode would go through a primary carbonium ion which is less stable than tertiary and in fact no trace of this compound could be found.



[208]

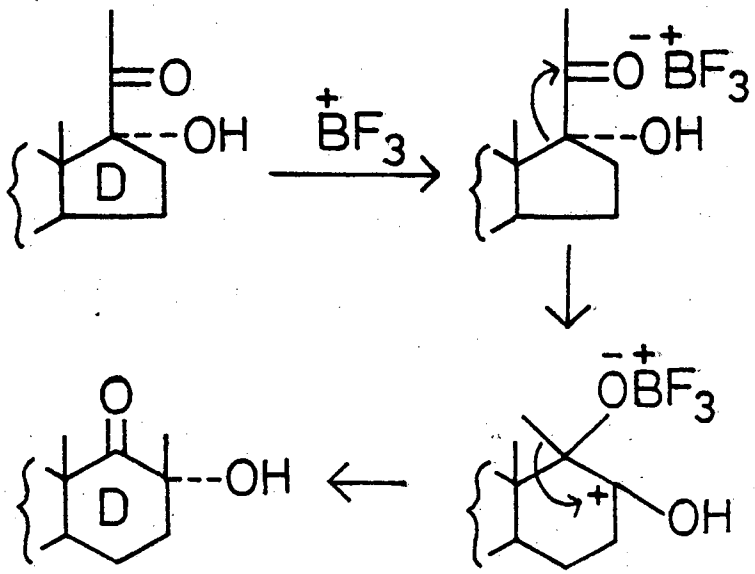


[209]

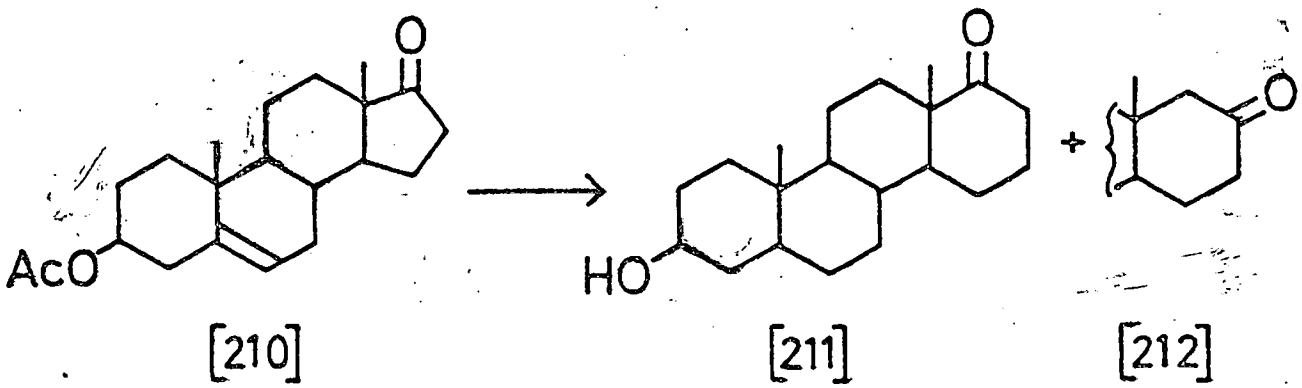
A variation of this reaction, rearranging the 17a-tosyl hydrazones of ring-D expanded steroids leading to the C-homo derivatives appeared a possibility.

The D-homo steroids prepared were of two types. D-Homo-androstenolone was prepared by the Tiffeneau-Demjanov rearrangement route [49,50,52,117,118] starting from androstenolone. Scheme 64 . The 17a-keto epimer was separated from its 17-keto epimer (212) by column chromatography, the 17a-keto epimer being formed in 6:1 ratio with the 17-keto epimer in line with previous results.

The second D-homosteroid, 3β,17α-dihydroxy-17β-methyl-D-homoandrost-5-en-17a-one(214) was prepared by a pinacol-pinacolone, Scheme 66 , rearrangement of the 17α-hydroxy-pregnenalone (213), Scheme 65 ,



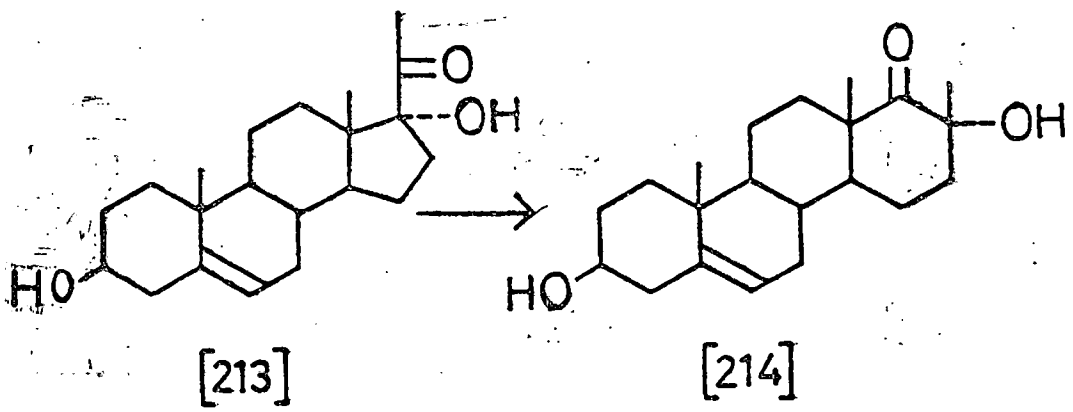
Scheme 66



Scheme 64

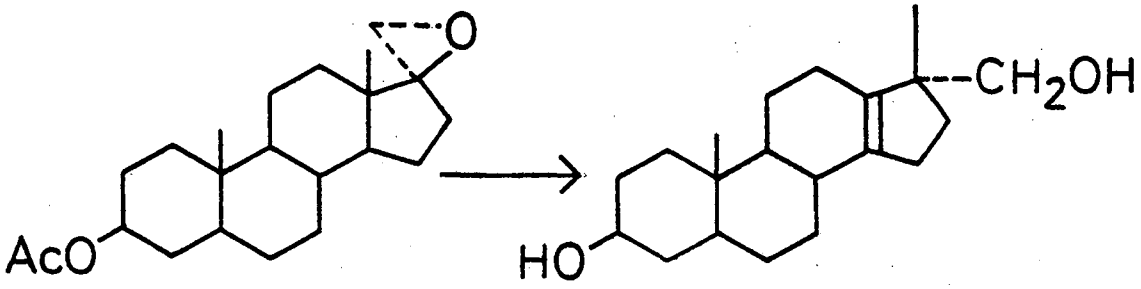
by reaction with boron-trifluoride etherate[119].

The 17-tosylhydazones of both androstenolone and D-homo-androstenol-17a-one (211) were prepared by refluxing the steroid with

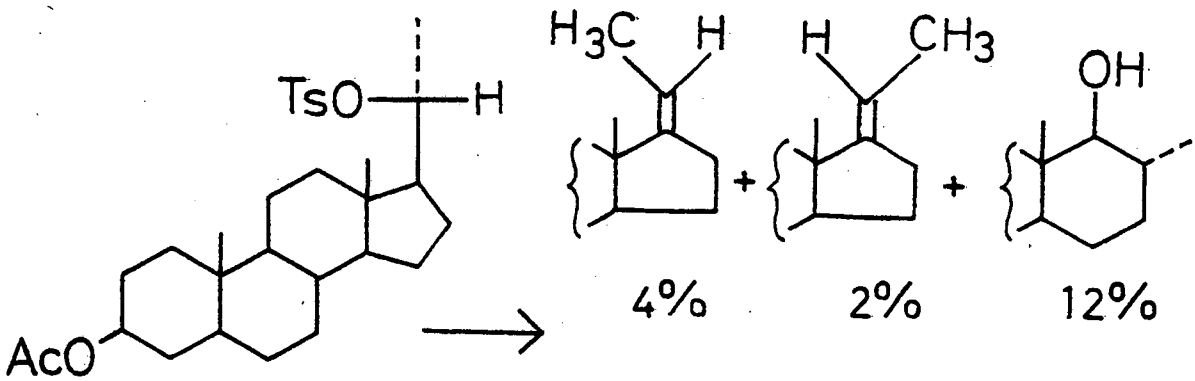


Scheme 65

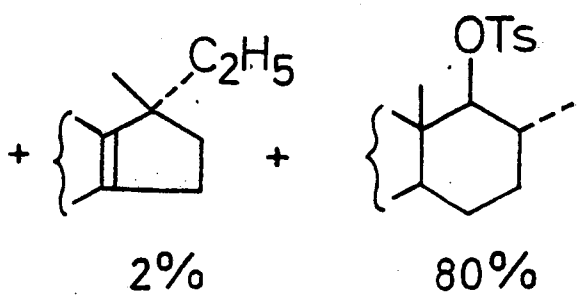
toluene-4-sulphonhydrazide in ethanol in the presence of catalytic amounts of concentrated hydrochloric acid. The corresponding 17-tosylhydrazone of 3β-17α-dihydroxy-17β-methylandrost-5-en-17a-one did not form however, even with prolonged refluxing, due to the hindrance by the two axial C-18 and C-17 methyl groups.



[218]



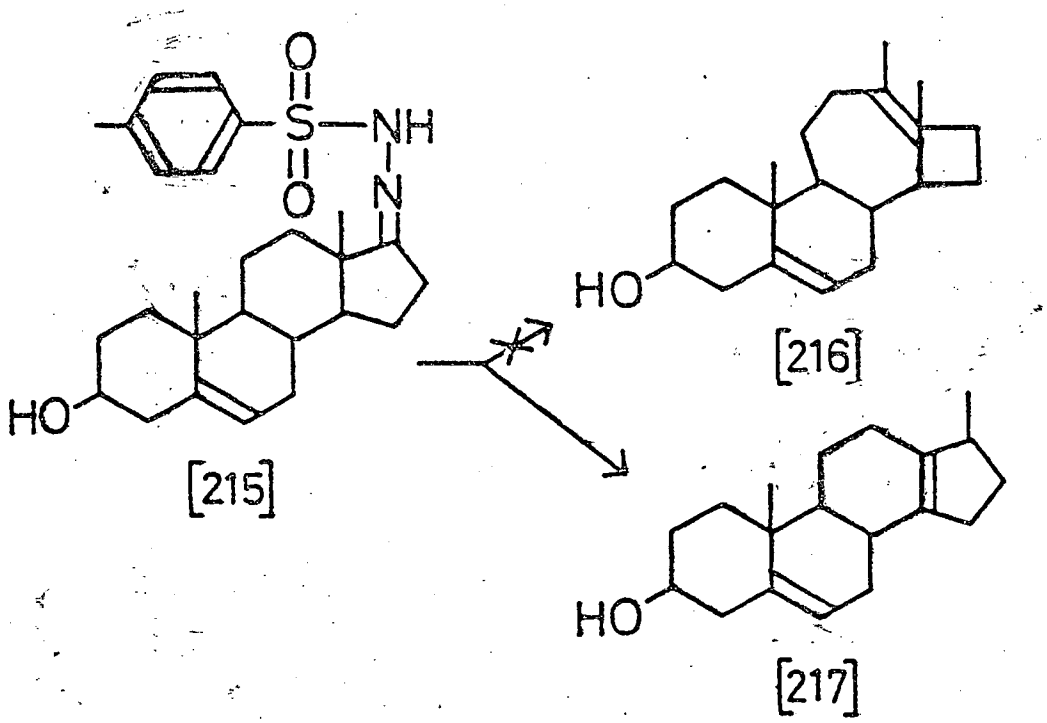
[219]



[220]

Scheme 68

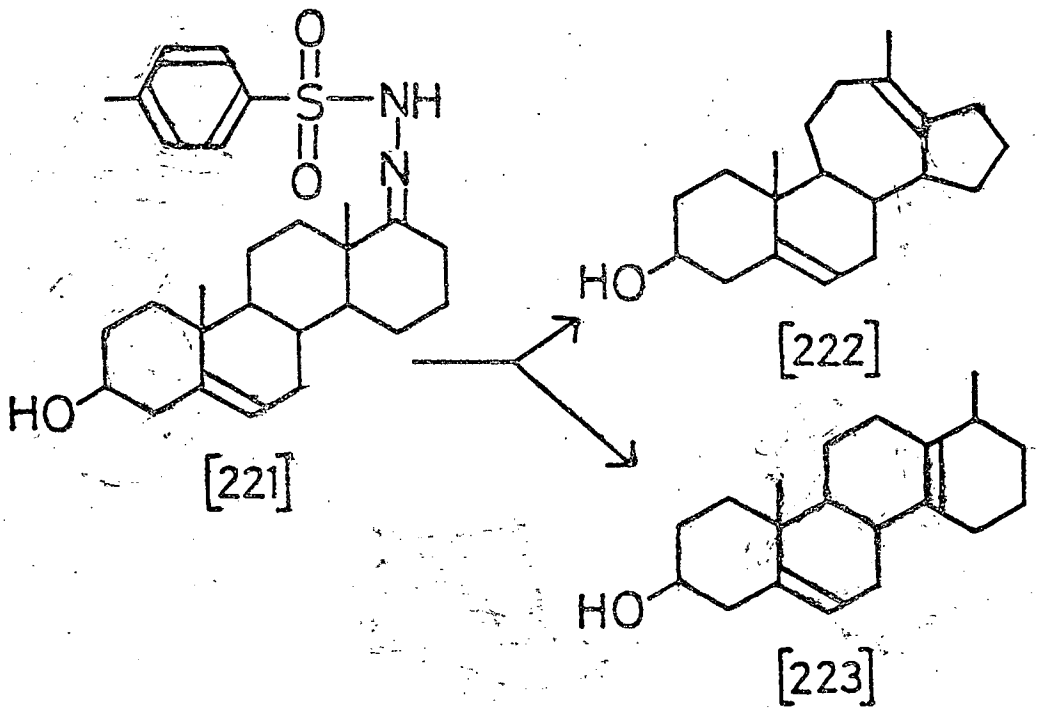
Rearrangement of the tosylhydrazone of androstenolone (215) with base in digol at 180°C gave a major product whose mass spectrum showed a molecular ion at $^{m}/_{e}$ 272 (100%). Thin-layer chromatography showed three minor products. Although the conditions for Wagner-Meerwein rearrangement were satisfied, the four coplanar centres being N-C17-C13-C14, the final product would have a four membered ring-D adjacent to a seven membered ring-C with a double bond at the junction of these two rings (216). This highly strained species was very unlikley, this being confirmed by the n.m.r. spectrum which showed one angular methyl signal at τ8.96 due to the C-19 methyl and a doublet at τ9.02 and τ9.08 which indicated that migration of the C-18 methyl to the C-17 position had occurred with the formation of a double bond at C13-C14 (217). Scheme 67 .



Scheme 67

This C-18 methyl migration has been shown in treatment of exocyclic epoxides (218) of ring-D with strong acid[67] and in D-homo steroid formation by treatment of a 20-tosylate (219) with florisil which gave the product of C-18 methyl migration (220) in 2% yield. Scheme 68.

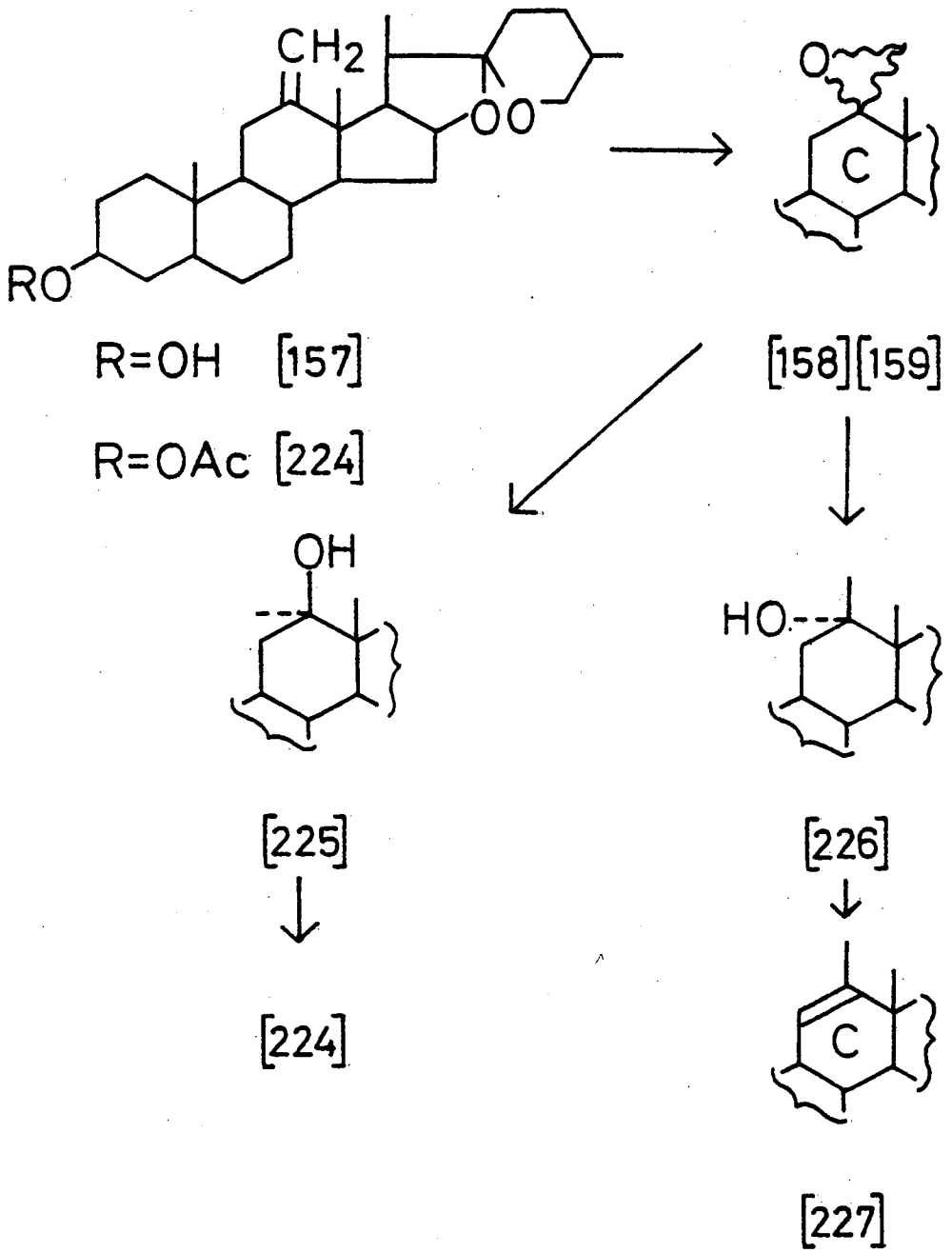
Similar treatment of the tosylhydrazone of D-homoandrosten-ol-17a-one (221) gave a mixture inseparable by chromatography and by attempted crystallisation of at least three different components, the mass spectrum of which showed a molecular ion at $^{m}/_{e}$ 286 (30%) corresponding to either the C-homo rearrangement product (222) or the derivative from C-18 methyl migration (223). Scheme 69 . The n.m.r. spectrum was complicated by the presence of several different products and so could



Scheme 69

give little insight into their nature, peaks appearing at τ 8.99 due to the C-19 methyl and τ 9.24, τ 9.16, τ 8.45, τ 8.36 and τ 8.21, one of the three signals at lower field possibly being due to the C-12a methyl adjacent to the double bond (222).

Attention was turned to the 17a-exocyclic epoxides of D-homo steroids and their possible rearrangement products. Coxon et al.[70] isolated the 12α,12'-epoxide of hecogenin (158) by column chromatography on alumina of the epoxide mixture formed by reaction of monoperphthalic acid

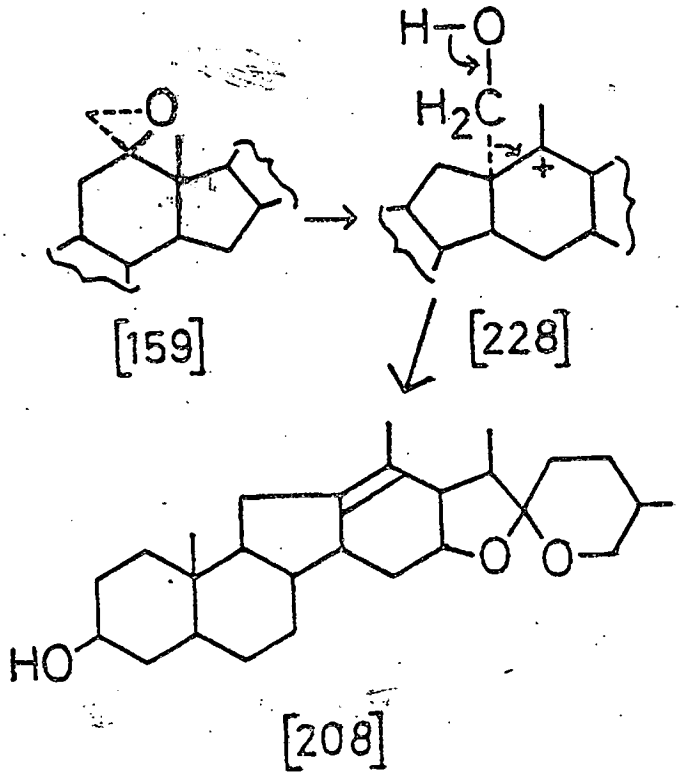


Scheme 70

on 12-methylene-tigogenin (157). The configuration was assigned from following the course of the dehydration of the tertiary alcohols obtained by reducing the epoxide with lithium aluminium hydride and reacetylating to give the 3β-acetoxy product but not the 12-acetoxy. Dehydration of the 12α-hydroxy-12β-methyl epimer (158) with thionyl chloride-pyridine gave the Δ^{11}-olefin (227) in 80% yield resulting from the favourable trans-diaxial elimination of a water moiety. The 12β-hydroxy-12α-methyl epimer (159) underwent the expected smooth elimination to give the 12-methylene-tigogenin acetate (224) in high yield. Scheme 70 .

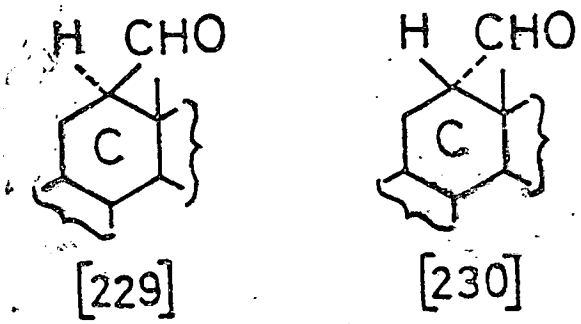
As with the corresponding tosylhydrazones, these epoxides were found to rearrange giving a C-nor-D-homo $\Delta^{13(17a)}$ olefin (208). The rearrangement takes place on treatment with either boron-trifluoride etherate or p-toluene sulphonic acid. The rearrangement was envisaged as proceeding through cleavage of the C12-O bond and migration of the electron pair of the C13-C14 bond forming a carbonium ion intermediate (228) fragmentation of which led to the $\Delta^{13(17a)}$ olefin (208) with loss of formaldehyde. Scheme 71 .

While the electron shifts involved in the transformation of the 12β,12'-epoxide (159) into the intermediate (228) and the 12β-aldehyde (229) which is also formed in the reaction with boron-trifluoride, could be concerted with the cleavage of the C12-O bond, the formation of both the 12β-aldehyde (229) and the $\Delta^{13(17a)}$ olefin (208) in modest proportions from the 12α,12'-epoxide (158) requires the intermediacy of a discrete C-12 carbonium ion, since the stereochemical requirements for a synchronous rearrangement are not filled in this case. The product of concerted hydride migration in the 12α,12'-epoxide would be the 12α-aldehyde (230), the less stable epimer. It is therefore concluded that the reaction pathway involving a carbonium ion intermediate can compete effectively with the concerted



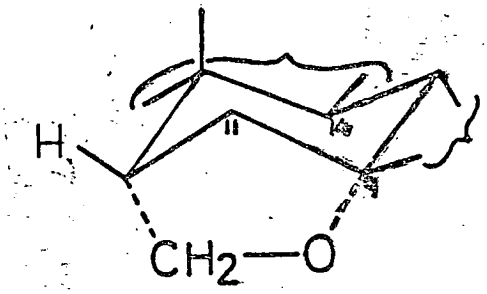
-Scheme 71

rearrangement when the latter leads to the less stable epimer.



Perchloric acid rearrangement of the β-epoxide gave no hydroxyl, ketone or aldehyde functions or unsaturation in the minor products but in fact a cyclic ether (231) n.m.r. evidence leading to this structure. The α-epoxide gave both the cyclic ether and 12β-aldehyde (229). The product

ratios observed for these epoxy systems implied that the free energy of activation for carbonium ion processes is only very slightly greater



[231]

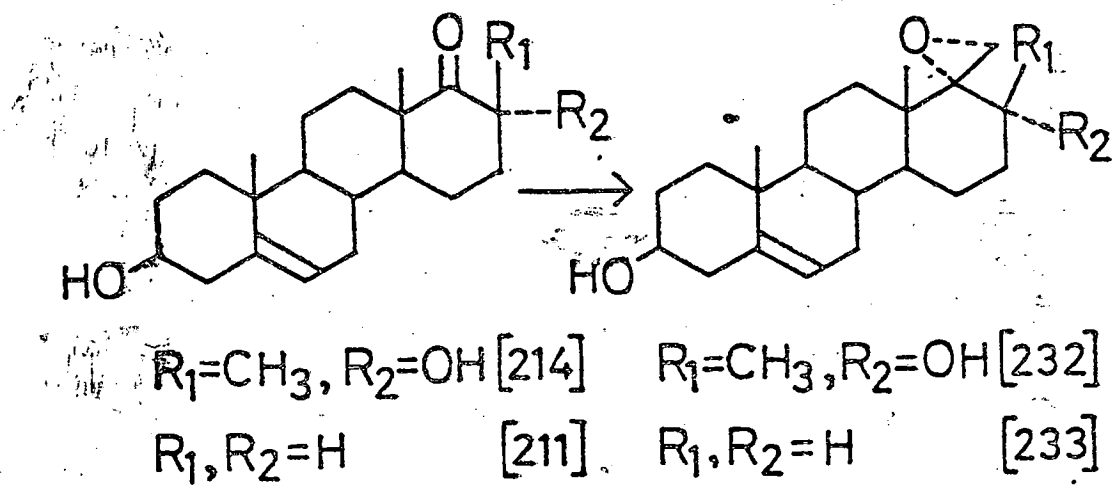
than for concerted hydride migration leading to aldehydes. The results are summarised in Table 9.

Reactants		Products				
		Solvent	13(17a) (208)	β-aldehyde (229)	α-aldehyde (230)	cyclic ether (231)
α-epoxide (158)	BF_3	Benzene	20%	35%	32%	
		ether	30%	29%	41%	
	perchloric acid			11%		68%
β-epoxide (159)	BF_3	Benzene	33%	45%		
		ether	36%	50%		
	perchloric acid		81%			19%

Table 9

The epoxides of both D-homoandrostenol-17a-one (233) and the 3β,17α-dihydroxy-17β-methyl-D-homoandrostenol-17a-one (232) were prepared in good yields by reaction of the parent ketones with trimethyl sulphoxonium iodide. Thin layer chromatography showed two minor factions

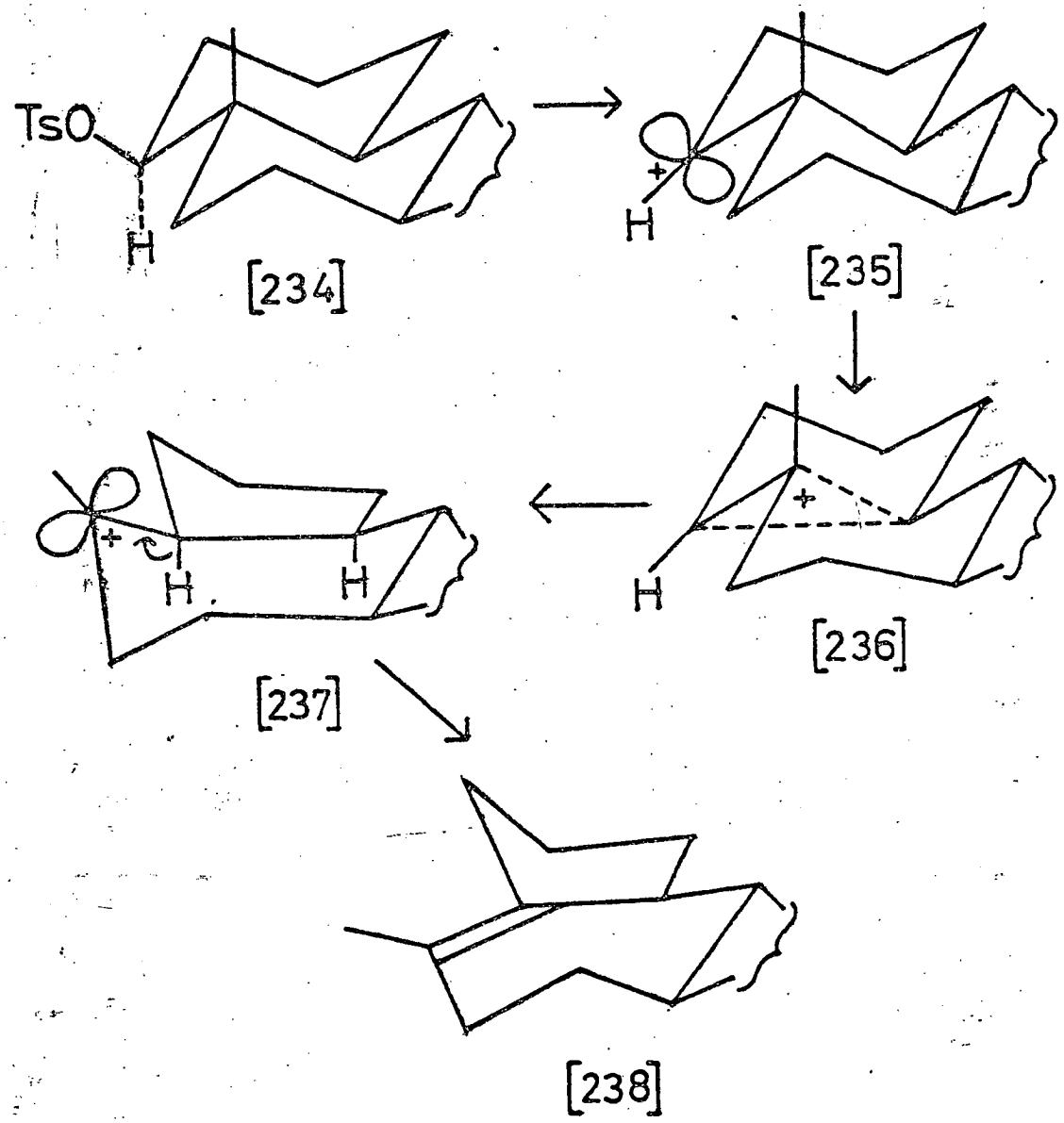
which were removed by recrystallisation from methanol. The 17α,17a' configuration, Scheme 72, was assigned to the epoxides from experience of product ratios of similar reactions.[118] Only one signal appears in the n.m.r. spectrum for each angular methyl of the recrystallised epoxide whereas the position of the C-18 methyl signal varies with the two different oxiran configurations at C-17 in androstenolone which would be expected for the D-homo species if both epimers were in fact present. Because of this configuration, any rearrangement by a concerted process must be ruled out since O-C17a-C13-C14 must be coplanar in accord with Wagner-Meerwein if a C-homo skeleton is to be formed by C13-C14 bond migration.



Scheme 72

Recent work by Khattak et al.[120] and Hirschmann[121] on the solvolysis of D-homotosylates has shown that under certain conditions, rearrangement takes place resulting in the formation of a C-homo-$\Delta^{13(17)}$ olefin. The process has no anchimeric assistance due to C13-C14 bond migration to form the carbocation (236) although this cation is likely to play an important part in the formation of the final products. The mode of reaction was interpreted as an unassisted ionisation of a tosylate to give a classical carbocation (235) which may subsequently undergo bond

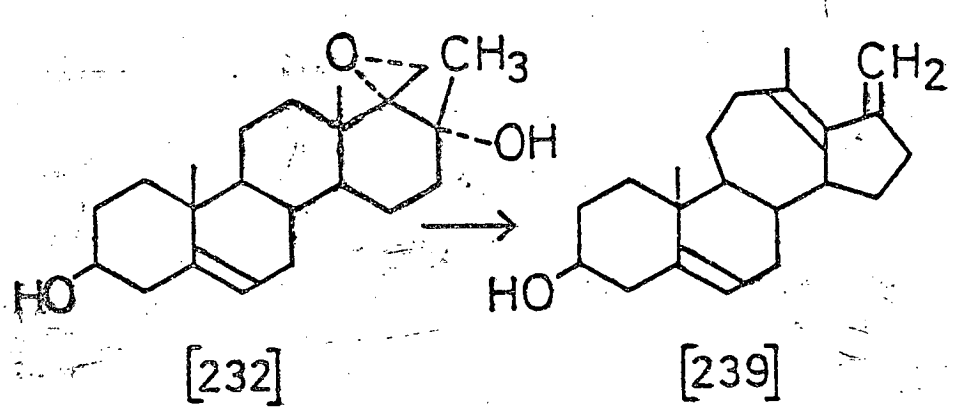
delocalisation forming the non-classical structure (236) from which the final products are derived[122,123]. Scheme 73.



Scheme 73

Rearrangement of the epoxide 17aα-17a'-epoxy-3β.17α-dihydroxy-17β-methyl-D-homoandrost-5-ene (232) was carried out using boron trifluoride etherate in both benzene and ether solvents as well as with toluene-4-sulphonic acid in refluxing benzene. Gas chromatography of the reaction mixtures showed three components present in both reactions with boron

trifluoride in ratios of 6:6:1. Column chromatography failed to separate the components but the mass spectra show the appeareance of a peak at $^{m}/_{e}$ 298 assigned to the rearranged adduct with the loss of water due to the dehydrating nature of both boron trifluoride or by instant loss of water moiety in the mass spectrometer. The n.m.r. spectrum, although complicated by the presence of a mixture, shows a new olefinic peak at τ4.40. This is assigned to an exocyclic methylene at C-17 formed by dehydration of the 17α-hydroxyl and therefore equatorial configuration with a 17β-methyl proton. Scheme 74 . A broad singlet also appears at τ8.42 assigned to the 12a-methyl adjacent to the double bond.



Scheme 74

Rearrangement of the epoxide with toluene-4-sulphonic acid yielded a mixture of products as a red gum, the components of which appeared as one broad peak with a small peak adjacent to it in the g.l.c. The mass spectrum again shows a peak at $^{m}/_{e}$ 298. An exact mass calculation for $C_{21}H_{30}O$ gives 298.229654, and that found was 298.230045, an error of less than 2 p.p.m.

No evidence could be found for the presence of aldehyde products, the mass spectrum of which would have a molecular ion at $^{m}/_{e}$ 346 or $^{m}/_{e}$ 328 if dehydration took placeneither of which appear, the only other significant

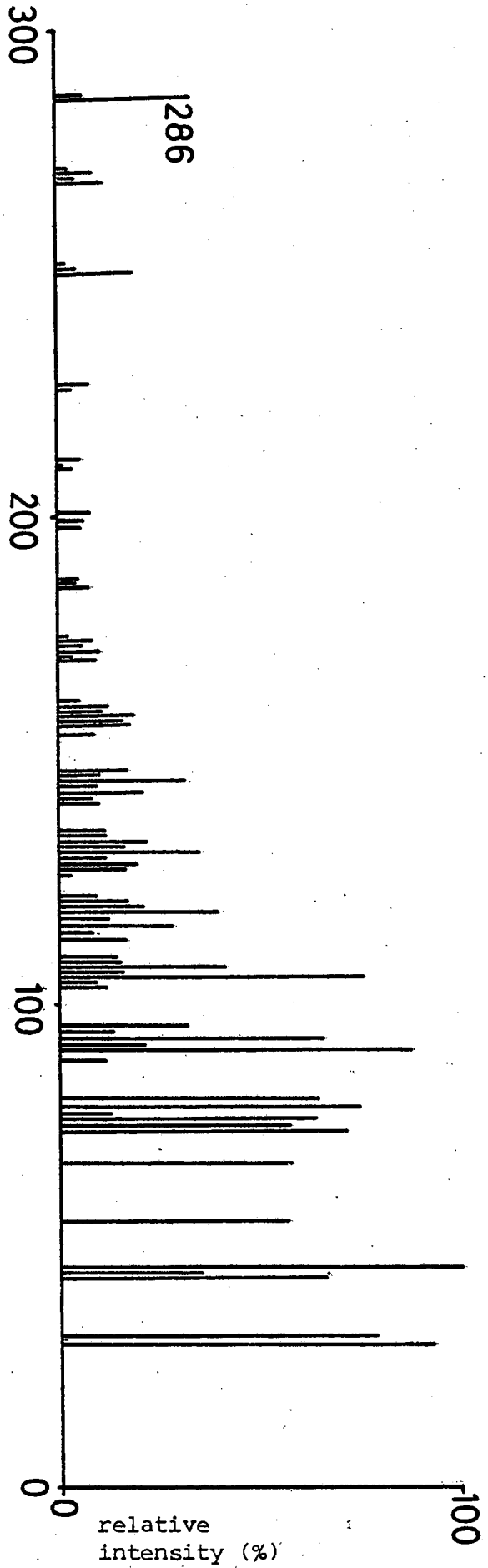
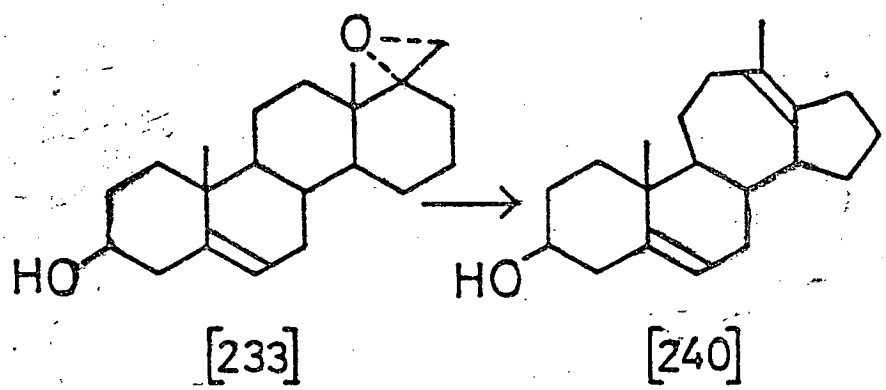


fig. 6 Mass spectrum of 3β-hydroxy-12a-methyl-18-nor-C-homo-androsta-5, 12a,(13)-diene (222)

peaks in this region being $^{m}/_{e}$ 356 and $^{m}/_{e}$ 338 which are due to a carbonyl impurity in the starting material shown by the mass spectrum and infra-red spectrum.

Rearrangement of 17α-17'-epoxy-3β-hydroxy-D-homoandrost-5-ene (233) with boron-trifluoride etherate in benzene overnight gave a red gum, the n.m.r. spectrum of which showed the appearance of a methyl signal at τ8.27 with further methyl signals at τ9.18, τ9.00 and τ9.08, the latter of which had a shoulder. Treatment of the epoxide with toluene-4-sulphonic acid again gave a yellow semi-crystalline product which showed a new methyl signal at τ8.27 with other methyl peaks at τ9.18, τ9.00 and τ9.08, the shoulder on which was better resolved than before. The methyl peak at τ8.27 was assigned to the olefinic methyl of a C-homo-18-nor steroid (240). Scheme 75.

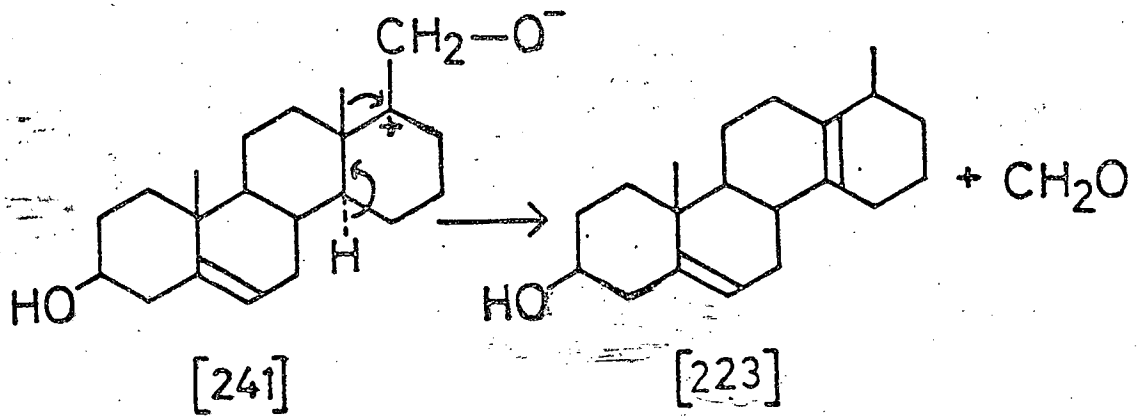


[233] [240]

Scheme 75

The mass spectra of the mixtures showed a peak at $^{m}/_{e}$ 286 (36%) assigned as the molecular ion of the product of C13-C14 bond shift (240). Fig.6. The two methyl peaks not assigned to this product could be a doublet from C-18 methyl migration to C-17a (242) which would give the same molecular ion in the mass spectrum.

So from the nature of the products and starting materials the reactions are envisaged as starting with the breaking of the C17a-O bond



Scheme 76

of the epoxides by the reagents forming a discrete carbonium ion intermediate (241) followed by bond delocalisation to give the non-classical carbocation (236) proposed by Khattak et al. from which the final products are derived by loss of a formaldehyde moiety. Lack of aldehydes in the products rules out any concerted hydride migration. Scheme 76.

From inspection of Dreiding models, it was seen that the initial migration of the C13-C14 bond to form the C-homo structure must occur in the sense which leads to a cis-fusion of rings-C and -D in the 12a-carbocation (237) and a model shows that the conformation in which this ion is initially formed involves a considerable increase in compression between the C-7 and C-15 positions, the 7,8- and 14,15-bonds becoming very nearly eclipsed. The driving force for the rearrangement therefore presumably comes from the conversion of a secondary into a tertiary carbocation. Non-reversion of the rearranged olefinic intermediates to the normal 13β-D-homo androstane skeleton is probably due to the fact that microscopic reversibility demands that a return to the original 13β-configuration should proceed through 13α-protonation of the olefin (238) to the same strained cation, as well as being contrary to the trend of cation stabilities.

4.2 Experimental Section

A Preparation of D-Homodehydroisoandrostenol-17a-one by Tiffeneau-Demjanov reaction route

4.2.i 3β-Acetoxy-17-cyano-17-hydroxy-androst-5-ene

a. Reaction of dehydroisoandrostenolone acetate with potassium cyanide[124,50]

To a stirred mixture of dehydroisoandrostenolone acetate (6g) and potassium cyanide (36g) in absolute alcohol (200ml) at 10°C was added acetic acid (38.5 ml) over a 40 minute period. The mixture was then stirred for 1 hour at 10°C then 2 hours at room temperature. Addition of water precipitated a solid which was filtered off and was washed with 2% acetic acid then dried *in vacuo*. T.l.c. of the white solid (6.12g) showed two spots, one of which corresponded to starting material. This was eluted first from an alumina column with benzene (2.88g, 47%). The 3β-acetoxy-17-cyano-17-hydroxy-androst-5-ene (3.24g, 53%) was eluted with ethanol, m.p. 118-122°, (lit.,[124], 124°); ν_{max} 3530, 3000, 1720, 1250cm^{-1}; n.m.r. (60MHz) τ 9.05 (C-18 *methyl*), 8.94 (C-19 *methyl*), 7.94 (C-3β *acetoxy*), 4.62 (m, $W_{\frac{1}{2}}$ = 5 Hz C-6 *proton*).

b. Reaction of dehydroisoandrostenolone with acetone cyanohydrin[10,125]

Dehydroisoandrostenolone (1g) was dissolved in ethanol (10ml) and undistilled acetone cyanohydrin (1ml) added. The mixture was heated under reflux with triethylamine (0.5ml). After 1 hour, the precipitate which had formed was filtered off and washed with water then dried *in vacuo* to leave a white solid (207 mg, 38%); ν_{max} 3500, 2900cm^{-1} acetylation of which gave 3β-acetoxy-17-cyano-17-hydroxyandrost-5-ene (225 mg); m.p. 119-125°. The infra-red and n.m.r. spectra were consistent with those for the required product as in 4.2.i.a.

4.2.ii 17-Aminomethyl-3β,17-dihydroxy-androst-5-ene[53]

3β-Acetoxy-17-cyano-17-hydroxy-androst-5-ene (3.0g) was dissolved in anhydrous ether (50ml), which was added dropwise to a slurry of lithium aluminium hydride (3.0g) in refluxing dry ether (100ml). After addition was complete, the reaction mixture was refluxed for 2 hours, the excess lithium aluminium hydride was then destroyed by the careful addition of water. Addition of dilute sulphuric acid (10ml) afforded two clear layers. The organic layer was dried over magnesium sulphate, filtered and evaporated to dryness giving a white solid (2.65g). T.l.c. showed two minor impurities corresponding to dehydroepiandrostenolone and 3β-acetoxy-17-cyano-17-hydroxy-androst-5-ene which were removed by crystallisation from methanol giving the pure 17-aminomethyl-3β,17-dihydroxy-androst-5-ene mixture (1.4g, 52%); ν_{max} 3600, 3500, 2900, 1685cm^{-1}; n.m.r. (60 MHz) τ 9.25 (C-18 methyl), 8.98 (C-19 methyl).

4.2.iii D-Homodehydroisoandrostenol-17a-one[51] (211)

17-Aminomethyl-3β,17-dihydroxy-androst-5-ene (812mg) was dissolved in glacial acetic acid (15ml) and ether (5ml) and the solution was cooled to -10°C. A solution of sodium nitrite (2.0g) in water (10ml) was added dropwise, the temperature never being allowed to rise above 5°C. After complete addition, the mixture was stirred at 0°C for 3 hours. Addition of water precipitated a solid which was extracted into ether, the ethereal solution was washed with 5% sodium bicarbonate, dried over magnesium sulphate, filtered and evaporated to dryness to give a pale yellow solid (685mg). Column chromatography on alumina afforded D-homodehydro-isoandrostenol-17a-one (577mg, 74%); m.p. 179-181° (lit.,[51] 180-1°); ν_{max} 3600, 1695, 1615cm^{-1}; n.m.r. (60 MHz) τ 8.99 (C-19 methyl), 8.87

(C-18 methyl), 6.42 (m, $W_{\frac{1}{2}}$ = 20 Hz, H-3), 4.67 (m, $W_{\frac{1}{2}}$ = 8 Hz, H-6).

B Preparation of D-homodehydroisotandrostanol-17a-one via the exocyclic epoxides of D.H.A.

4.2.iv 17,20-Epoxy-21-nor-17-pregn-5-en-3β-ol[66,67,118]

Sodium hydride suspension (60% in oil; 12g) was washed with petroleum-ether (40-60°) and stirred in dimethyl formamide (300ml) to form a fine suspension. Finely divided crystalline trimethyl sulphoxonium iodide (35g) was added in small portions. When hydrogen evolution had almost ceased, dehydroisoandrostenolone acetate (10g) was added. The mixture was stirred at room temperature for 16 hours then poured into ice-cold water (21). The precipitated steroid was filtered off and washed with water then dried in vacuo leaving 17,20-epoxy-21-nor-17-pregn-5-en-3β-ol mixture (8.3g, 91%); ν_{max} 2600, 3420, 1043cm^{-1}; n.m.r. (60 MHz) τ 9.16 (C-18 methyl) of α-epoxide), 9.10 (C-18 methyl of β-epoxide), 8.97 (C-19 methyls), 7.45, 7.33, 7.29, 7.13, 7.05 (d,d, J=5Hz, C-20 epoxy methylenes) 4.66 (m, $W_{\frac{1}{2}}$ = 14 Hz, 6-H).

4.2.v 20-Azido-21-nor-7α-pregn-5-ene-3β,17-diols[66,67,118]

17,20-Epoxy-21-nor-17-pregn-5-en-3β-ols (8.0g) in dimethyl-formamide (200ml) was heated under reflux for 3 hours with sodium azide (8.0g) and boric acid (8.0g). The suspension was then poured into ice-cold water and the resulting precipitate was washed with water and dried in vacuo. Recrystallisation from acetone-petether (40-60°) gave the 20-azido-21-nor-7α-pregn-5-ene-3β,17-diols as a white solid (7.8g, 85%) m.p. 121-128° (lit.,[67] 133-134°); ν_{max} 3600cm^{-1}; n.m.r. (60MHz) τ 9.24

(C-18 methyl of 17α-ol), 9.09 (C-18 methyl of 17β-ol), 8.97 (C-19 methyls), 6.92, 6.73, 6.56, 6.36 (d,d. J = 12 Hz, C-20-CH$_2$), 4.66 (m, $W_{\frac{1}{2}}$ = 14Hz H-6); mass spectrum, $^{m}/_{e}$ 345 (M^+, 14%), $^{m}/_{e}$ 317 (60%), $^{m}/_{e}$ 271 (100%), $^{m}/_{e}$ 253 (89%) $^{m}/_{e}$ 289 (92%).

4.2.vi D-Homodehydroandrostenol-17a-one[66,67,118](211)

The 20-azido-21-nor-7a-pregn-5-ene-3β,17-diols (7.5g) in acetic acid (75ml) were stirred with zinc powder for 20 minutes after which time evolution of gas had ceased. Water (350 ml) and acetic acid (40ml) were then added. After filtration, the aqueous acidic solution was extracted twice with ether (200ml) and the extracts were combined and washed twice with water (100ml) and the aqueous washings added to the acidic layer. This solution was cooled in ice and sodium nitrite (4g) was added. After 3 hours the precipitate which had formed was extracted with ethyl acetate. The organic extracts were dried over magnesium sulphate, filtered and evaporated to dryness to give a mixture of D-homodehydroisoandrostenol-17a-one and D-homodehydroisoandrostenol-17-one as a white solid (3.96g). Column chromatography on alumina and elution with benzene-petether gave D-homodehydroisoandrostenol-17a-one (3.32g, 50%); m.p. 176-179° (lit.[51] 180-1); ν_{max} 3600, 1695, 1615cm^{-1}; n.m.r. (60 MHz) τ8.99 (C-19 methyl), 8.87 (C-18 methyl), 6.42 (m, $W_{\frac{1}{2}}$ = 19 Hz, H-3), 4.67 (m, $W_{\frac{1}{2}}$ = 8 Hz, H-6).

C Preparation of a D-homosteroid by a Pinacol-Pinacolone rearrangement

4.2.vii 17α-Hydroxy-17β-methyl-D-homodehydroisoandrostenol-17a-one[119](214)

17α-Hydroxy-pregnenolone acetate (1.6g) in acetic acid (160ml) was treated with acetic anhydride (6.4ml) and freshly distilled boron trifluoride etherate (6.4ml) and allowed to stand at room temperature for 18 hours. After this time, water (160ml) was added and the resulting precipitate extracted with ether. The ethereal solution was washed with 10% potassium bicarbonate, dried over sodium sulphate, filtered and evaporated to dryness to give 17α-hydroxy-17β-methyl-D-homodehydroisoandrostenol-17a-one as a white solid (1.54g, 96%), t.l.c. of which showed one spot only. ν_{max} 3450, 2950, 1736, 1250cm^{-1}; n.m.r. (60MHz)τ 8.65 (C-18 methyl), 8.62 (C-19 methyl), 8.53 (C-17β methyl), 7.97 (C-3β acetoxy), 4.66 (m, $W_{\frac{1}{2}}$= 15Hz, H-6).

D Preparation of D-homoketone derivatives

4.2.viii Tosyl Hydrazone of D-homodehydroisoandrostenol-17a-one (221)

D-Homodehyroisoandrostenol-17a-one (700mg) was dissolved in carbon tetrachloride (8ml) and toluene-4-sulphonhydrazide (600mg) in ethanol (10ml) and concentrated hydrochloric acid (0.5ml) added. After 30 minutes at room temperature, the mixture was warmed on the steam bath and a precipitate formed which was filtered off, was washed with water and dried *in vacuo* to give the tosylhydrazone of D-homodehydroisoandrostenol-17a-one as a white crystalline solid (432mg, 39%); m.p. 192-199° (decomp); n.m.r. (60MHz)τ 9.07 (C-18 methyl), 9.03 (C-19 methyl), 7.52 (tosyl methyl),

4.73 (m,$W_{\frac{1}{2}}$=6Hz,6-H), 2.78, 2.65, 2.30, 2.15 (d,d, 9Hz,9Hz4 aromatic protons).

4.2.ix Reaction of 17α-hydroxy-17β-methyl-D-homodehydroisoandrostenol-17a-one with toluene-4-sulphonhydrazide

17α-Hydroxy-17β-methyl-D-homodehydroisoandrostenol-17a-one (520mg) was reacted with toluene-4-sulphonhydrazide (350mg) as described above, 4.2.viii. Even after prolonged warming on the steam bath (~4 hours) no precipitate formed. Addition of dilute sodium hydroxide and extraction with ether, drying the ether layer over magnesium sulphate, filtration and evaporation to dryness produced a white solid (337 mg), the t.l.c., infra-red and n.m.r. spectra of which showed it to be unreacted ketonic starting material.

4.2.x Reaction of Dehydroisoandrostenolone acetate with toluene-4-sulphonhydrazide

Dehydroisoandrostenolone acetate (4.50g) was suspended in ethanol (150ml) and toluene-4-sulphonhydrazide (3.50g) was added and the mixture was heated under reflux for 30 minutes with concentrated hydrochloric acid (2ml). The mixture was then poured into ice-cold water and the resulting precipitate was filtered off, washed with 2 N sodium hydroxide then water and dried *in vacuo* to give the tosylhydrazone of dehydroisoandrostenolone acetate as a white crystalline solid (4.83g, 72%). m.p. 204-211° (decomp); n.m.r. (60MHz) τ 9.22 (C-18 methyl), 9.00 (C-19 methyl), 7.93 (C-3β acetoxy), 7.60 (tosyl methyl), 4.73 (m,$W_{\frac{1}{2}}$=6Hz, 6-H), 2.86, 2.72, 2,32, 2,18 (d,d H=9Hz,4 aromatic protons).

4.2.xi 17a,20-Epoxy-21-nor-17aα-D-homopregn-5-en-3β-ol(233)

This exocyclic epoxide of D-homodehydroisoandrostenol-17a-one was prepared as described above, 4.2.iv, by reaction of D-homodehydroisoandrostenol-17a-one (1.5g) with trimethylsulphoxonium iodide (6g) and sodium hydride (3g) in dimethyl formamide (50ml). The reaction mixture

was poured into ice-cold water and the precipitate so formed filtered off, washed with water and dried *in vacuo*. Recrystallisation from methanol gave 17a,20-epoxy-21-nor-17aα-D-homopregn-5-en-3β-ol as a white solid (1.06g, 67%) m.p. 135-142°; n.m.r. (60MHz)τ 9.06 (C-18 methyl), 8.97 (C-19 methyl), (d,d, J=5Hz,C-20-CHz-), 4.68 (m,$W_{\frac{1}{2}}$ = 6Hz,6-H); mass spectrum, $^{m}/_{e}$ 316 (M^+, 75%), $^{m}/_{e}$ 301 (M-15, 17%), $^{m}/_{e}$ 298 (M-18, 21%), $^{m}/_{e}$ 271 (100%).

4.2.xii 17aα,17a'-epoxy-3β,17α-dihydroxy-17β-methyl-D-homoandrost-5-ene(232)

This exocyclic epoxide was prepared as described above, 4.2.iv, by reaction of 17α-hydroxy-17β-methyl-D-homodehydroisoandrostenol-17a,one (2g) with trimethylsulphoxonium iodide (7.0g) and sodium hydride (2.4g) in dimethylformamide (30ml) at room temperature for 16 hours. The mixture was then poured into ice-cold water and the resulting precipitate extracted into ether. The ethereal solution was dried over magnesium sulphate, filtered and evaporated to dryness. Crystallisation from methanol gave 17aα,17a'-epoxy-3β,17α-dihydroxy-17β-methyl-D-homoandrost-5-ene as a white solid (1.49g, 72%), m.p. 132-135°, n.m.r. (60MHz) τ 9.03 (C-18 and C-19 methyls), 8.50 (C-17β methyl), 7.83, 7.70 (d,d J=5Hz, C-20-CH2-), 4.66 (m,$W_{\frac{1}{2}}$=5Hz,6-H); mass spectrum, $^{m}/_{e}$ 346 (M^+, 100%).

E Rearrangements of D-ring ketonic derivatives [126]

4.2.xiii Rearrangement of tosylhydrazone of dehydroisoandrostenolone acetate

The tosyl hydrazone of dehydroisoandrostenolone acetate (2.5g) was dissolved in digol (80ml) and sodium hydroxide (3.0g) in water (20ml) was added. The solution was then heated under nitrogen to 100°C, the nitrogen flow was stopped and at around 120°C, rapid evolution of gas occurred, which ceased at around 160°C. The mixture was then cooled and

poured into ice-cold water and the product was extracted with ether. The ether layer was dried over sodium sulphate, filtered and evaporated to dryness to leave an oil. The t.l.c. showed one major component and four trace impurities. Column chromatography on alumina and elution with various solvent systems failed to separate the components completely, each fraction showing varying degrees of purity of the main component. The purer fractions were combined and evaporated to dryness giving a light brown oil (1.14g); n.m.r. (60MHz)τ 9.08, 9.02 (d, J=4 Hz,C-17β methyl), 8.96 (C-19 methyl), 4.63 (m,$W_{\frac{1}{2}}$ = 5Hz 6-H); mass spectrum, $^{m}/_{e}$ 272 (M^{+}, 100%), $^{m}/_{e}$ 257 (M-15, 14%), $^{m}/_{e}$ 254 (M-18, 22%), $^{m}/_{e}$ 239 (M-33, 36%), 3β-hydroxy-17β-methyl-18-nor-androsta-5,13(14)-diene (217)

4.2.xiv Rearrangement of tosylhydrazone of D-homodehydroisoandrostenol-17a-one

The tosyl hydrazone of D-homodehydroisoandrostenol-17a-one (900mg) in digol (20ml) was heated to 180°C with sodium hydroxide (1.5g). After cooling, water was added to the reaction mixture and the resulting precipitate was extracted with ether, the ether layer was washed with water, dried over magnesium sulphate, filtered and evaporated to dryness to yield a pale yellow semi-crystalline solid (883mg). T.l.c. showed two main spots with at least three minor impurities; n.m.r. (60MHz)τ 9.24, 9.16, 8.99, 8.45, 8.36, 8.21; mass spectrum, $^{m}/_{e}$ 286 (M^{+}, 30%), $^{m}/_{e}$ 271 (7%), $^{m}/_{e}$ 268 (10%), $^{m}/_{e}$ 253 (17%), mixture of 3β-hydroxy-12a-methyl-18-nor-C-homoandrosta-5,12a(13)-diene (222) and 3β-hydroxy-17β-methyl-18-nor-D-homo-androsta-5,13(14)-diene (223).

4.2.xv Reaction of 17aα,17a'-epoxy-3β,17a-dihydroxy-17β-methyl-D-homoandrost-5-ene with boron trifluoride etherate in ether

The epoxide (1.6g) in anhydrous ether (160ml) was treated with boron trifluoride etherate (1.6ml) at 20°C overnight. The initial suspension

dissolved during the reaction. Water was then added and the ethereal layer was removed, dried over magnesium sulphate, filtered and evaporated to dryness to leave a dark red gum (12g), G.l.c. of the mixture showed three components in the ratio 6:6:1; n.m.r. (60MHz)τ 9.11 (C-19 methyl), 8.27 (C-12a methyl), 4.40 (C-17 exocyclic methylene); mass spectrum, $^{m}/_{e}$ 298 (M^{+}, 50%), 3β-hydroxy-12a-methyl-17-methylene-18-nor-C-homoandrosta-5, 12a(13)-diene (239); n.m.r. (60MHz)τ 9.11 (C-19 methyl), 9.01, 9.16 (d,J=11Hz C-17a methyl) 3β-hydroxy-17a-methyl-17-methylene-18-nor-D-homoandrosta-5, 13(14)-diene.

4.2.xvi Reaction of 17aα,17a'-epoxy-3β,17a-dihydroxy-17β-methyl-D-homoandrost-5-ene with boron trifluoride etherate in benzene

The epoxide (542mg) in anhydrous benzene (15ml) was treated with boron trifluoride etherate (1ml) at 20°C overnight. The solvent was then removed in vacuo to leave a yellow-brown solid (490mg), g.l.c. of which showed three components in ratio 6:6:1; n.m.r. (60MHz) is consistent with that for reaction mixture 4.2.xv; mass spectrum, $^{m}/_{e}$ 298 (M^{+}, 42%), 3β-hydroxy-12a-methyl-17-methylene-18-nor-C-homoandrosta-5,12a(13)-diene (239) and 3β-hydroxy-17a-methyl-17-methylene-18-nor-D-homoandrosta-5,13(14)-diene.

4.2.xvii Reaction of 17aα,17a'-epoxy-3β,17a-dihydroxy-17β-methyl-D-homoandrost-5-ene with toluene-4-sulphonic acid

The epoxide (288mg) was dissolved in anhydrous benzene (10ml) and refluxed for 30 minutes withtoluene-4-sulphonic acid (304mg). The reaction mixture was then cooled and water added. The steroid was extracted into ether, the ethereal solution dried over magnesium sulphate, filtered and evaporated to dryness to leave a red gum (214mg). G.l.c. showed one broad peak and one smaller peak in the ratio of approximately 30:1 mass spectrum, $^{m}/_{e}$ 298 (18%), calculated for $C_{21}H_{30}O$, 298.229654, found

298.230045, an error of less than 2 p.p.m, 3β-hydroxy-12a-methyl-17-methylene-18-nor-C-homoandrosta-5,12a(13)-diene (239).

4.2.xviii Reaction of 17a,20-epoxy-21-nor-17aα-D-homopregn-5-en-3β-ol with boron trifluoride etherate in benzene

The epoxide (240mg) in anhydrous benzene (5ml) was treated with boron trifluoride etherate (0.5ml) at 20°C overnight. The solvent was then removed in vacuo to leave a red gum (167mg); n.m.r. (60MHz)τ 9.08 (C-19 methyl), 8.27 (C-12a methyl); mass spectrum, $^{m}/_{e}$ 286 (M^{+}, 36%), $^{m}/_{e}$ 271 (M-15, 7%), $^{m}/_{e}$ 268 (M-18, 10%), $^{m}/_{e}$ 253 (M-33, 20%), 3β-hydroxy-12a-methyl-18-nor-C-homo-androsta-5,12a(13)-diene (222); n.m.r. (60MHz)τ 9.18, 9.13 (d, J=4Hz,C-17a methyl), 9.00 (C-19 methyl), 3β-hydroxy-17a-methyl-18-nor-D-homoandrosta-5,13(14)-diene (223).

4.2.xix Reaction of 17a,20-epoxy-21-nor-17aα-D-homopregn-5-en-3β-ol with toluene-4-sulphonic acid

The epoxide (310mg) was dissolved in anhydrous benzene (10ml) and thesolution heated under reflux with toluene-4-sulphonic acid (384mg) for 30 minutes. The reaction mixture was cooled, water was added and the steroid extracted with ether. The ethereal solution was dried over magnesium sulphate, filtered and evaporated to dryness to leave a yellow semi-crystalline product (184mg); n.m.r. (60MHz)τ 9.08, 8.27; mass spectrum $^{m}/_{e}$ 286 (M^{+}, 36%), 3β-hydroxy-12a-methyl-18-nor-C-homoandrosta-5,12a(13)-diene (222); n.m.r. (60MHz)τ 9.18, 9.13, 9.00; mass spectrum $^{m}/_{e}$ 286 (M^{+} 36%), 3β-hydroxy-17a-methyl-18-nor-D-homoandrosta-5,13(14)-diene (223).

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